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# ICU-ADMISSION, HOSPITAL LENGTH OF STAY AND RETURN TO WORK IN CRITICALLY ILL PATIENTS

– PRE- AND IN-HOSPITAL FACTORS

BY
SIGNE JUUL RIDDERSHOLM

DISSERTATION SUBMITTED 2018

AALBORG UNIVERSITY
DENMARK

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# - Pre- and in-hospital factors

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# Preface

This thesis is based on three studies carried out during my position as a PhD student at the Department of Anaesthesiology and Intensive Care, Aalborg University Hospital and affiliated to the Unit of Epidemiology and Biostatistics, Aalborg University Hospital, and the Department of Clinical Epidemiology, Aarhus University Hospital.

This work was made possible by a number of persons. First, I would like to thank my three supervisors: Bodil Steen Rasmussen for introducing me to research and for continuously encouraging and supporting me to continue research through soon eight years. Kristian Hay Kragholm for introducing me to programming and clinical epidemiology and always constructive and valuable feedback. Christian Fynbo Christiansen for his invaluable inputs and help with methodological challenges.

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Finally my warmest thanks goes to my husband Lars for his support, patience and taking good care of our children in my absence.

*Signe Juul Riddersholm, January 2018*

# List of papers

This dissertation is based on the following papers:

1. Riddersholm S, Kragholm K, Mortensen RN, Pape M, Hansen CM, Lippert FK, Torp-Pedersen C, Christiansen CF, Rasmussen BS. **Association of bystander interventions and hospital length of stay and admission to intensive care unit in out-of-hospital cardiac arrest survivors**. Resuscitation. 2017 Oct; 119:99-106. doi: 10.1016/j.resuscitation.2017.07.014. Epub 2017 July 15.

2. Riddersholm, Kragholm K, Mortensen RN, Moller Hansen S, Wissenberg, M, Lippert FK, Torp-Pedersen C, Christiansen CF, Rasmussen BS. **Organ Support Therapy in the Intensive Care Unit and Return to Work in Out-of-Hospital Cardiac Arrest Survivors – a Nationwide Cohort Study**. Resuscitation. 2018 jan; article in press, doi: 10.1016/j.resuscitation.2018.01.001. Epub 2018 January 11.

3. Riddersholm, Christensen S, Kragholm K, Christiansen CF, Rasmussen BS. **Organ Support therapy in the intensive care unit and Return to Work – a Nationwide, Register-based Follow-Up Study**. Manuscript draft.

# List of abbreviations:

AED: Automated external defibrillator

APACHE: Acute and chronic health evaluation

CI: Confidence interval

CPR: Cardiopulmonary resuscitation

DAG: Directed Acyclic Graph

EMS: Emergency medical service

HR: Hazard ratio

ICU: Intensive Care Unit

OHCA: Out-of-hospital cardiac arrest

OR: Odds ratio

PICS: Post Intensive Care Syndrome

PPV: Positive predictive value

RRT: Renal replacement therapy

SAPS: Simplified acute physiology score

SOFA: Sequential Organ Failure Assessment

# English summary

Intensive care is a central and very resource-intensive part of the health care system. In Denmark, approximately 30,000 patients are treated in an intensive care unit (ICU) each year. During the last decades it has become apparent that ICU-survivors suffer from several sequelae including physical and mental problems, reduced ability to participate in activities compared to before ICU-admission and decreased quality of life. To reduce risk of impairments and their consequences for the individual patient, both prevention of ICU-admission and identification of risk factors for severe impairments is important.

This thesis contains three cohort studies based on data from the National Patient registry, Civil registry, Danish cardiac arrest registry and DREAM. The purpose of the thesis was to investigate 1) Risk factors for ICU-admission and increased hospital length of stay among patients with out-of-hospital cardiac arrest (OHCA). 2) Impact of organ support on return to work among patients with out-of-hospital cardiac arrest. 3) Impact of the ICU-stay on return to work in a general ICU-population.

In study 1 we showed that among OHCA patients, bystander interventions such as CPR and defibrillation were associated with a reduction in hospital length of stay (LOS) and risk of ICU admission.

In the second study we showed that an increasing number of organ support in the ICU was associated with reduced rates of return to work. In this cohort particularly renal replacement therapy was associated with lower degree of return to work. Injuries following cardiac arrest are to a high extent caused by ischaemia, and our results may than indicate that organ failure reflects this damage and hereby is a predictor of possibility to resume activities as before arrest.

In the third study we showed that 68% of ICU-survivors returned to work within two years. In addition we found that mechanical ventilation and longer duration of ICU-stay, but not an increasing number of organ support or ‘Simplified Acute Physiology score’ (SAPS), were associated with delays and lower rate of return to work. Concurrently, disability benefits were common both among patients who never returned and patients who did return but thereafter left the workforce for a period of more than 4 weeks and patients who returned to work were not able to maintain salary as before ICU-admission.

In conclusion our studies show that in-hospital morbidity is reduced by pre-hospital early interventions among cardiac arrest patients, concurrently this morbidity is associated with unfavourable long-term outcomes.

# Dansk resume

Intensiv terapi er en central, men også særdeles ressource-forbrugende del af sundhedsvæsenet. I Danmark indlægges ca. 30.000 patienter årligt. De seneste årtier er det blevet klart at patienter der overlever intensiv terapi ofte har både fysiske og psykiske følger, nedsat evne til at deltage i aktiviteter som før indlæggelse, samt nedsat livskvalitet. For at nedsætte risikoen for senfølger samt de konsekvenser det intensive forløb får for den enkelte patient, er både forebyggelse af indlæggelse på samt identificering af risikofaktorer for svære følger vigtig.

Afhandlingen indeholder 3 kohortestudier baseret på data fra Landspatientregistret, CPR registret samt Dansk hjertestopregister og en forløbsdatabase fra beskæftigelsesministeriet (DREAM). Formålet med afhandlingen var at undersøge: 1) Risikofaktorer for intensivindlæggelse blandt patienter med hjertestop udenfor hospital, 2) Betydningen af organ-support for tilbagevenden til arbejde blandt hjertestoppatienter og 3) Betydningen af det intensive forløb for tilbagevenden samt vedligehold af arbejde hos den generelle intensivpatient.

I det første studie viste vi at præ-hospitale tiltag, såsom hjertelungeredning og defibrillering ved lægmand nedsætter både længden af det efterfølgende hospitalsophold samt risikoen for intensivindlæggelse blandt patienter med hjertestop udenfor hospital.

I det andet studie viste vi at en stigende grad af organsupport var associeret med en reduktion i arbejdsgenoptagelsen efter hjertestop udenfor hospital. Specielt akut dialyse var forbundet med en lav arbejdsgenoptagelse. Blandt hjertestoppatienter er organsvigt i høj grad en følge af iskæmi, og dermed kunne disse resultater indikere, at en højere grad af organskade afspejler den iskæmiske skade patienten har pådraget sig under sit hjertestop, hvorfor graden af organsvigt forudsiger hvor stor en chance patienten har for at genoptage sit liv som før hjertestop.

I det tredje studie viste vi at 68% af alle intensivpatienter, der overlever til hospitalsudskrivelse vender tilbage til arbejde indenfor to år. Vi fandt derudover at invasiv mekanisk ventilation og længere indlæggelsestid på intensiv, men ikke SAPS eller et stigende behov for organsupport var associeret med lavere grad af tilbagevenden. Samtidig viste vi i dette studie at sociale ydelser givet pga. sygdom var hyppige både blandt de der ikke vendte tilbage til arbejde, men også blandt de vendte tilbage men efterfølgende forlod arbejdsmarkedet i en længere periode og baldnt de der vendte tilbage til arbejde faldt årsindkomsten i de to første år efter intensivindlæggelse.

Sammenfattende viste vores studier, at tidlige præhospitale interventioner nedsatte den in-hospitale morbiditet hos hjertestoppatienter og at forskellige mål for in-hospital morbiditet, forudsiger tilbagevenden til arbejde efter kritisk sygdom for forskellige patientgrupper.

# Table of contents

# 1. Background

## 1.1 Introduction

Intensive care constitutes a central part of the health care system, caring for critically ill patients. In Denmark, we have more than 30.000 ICU admissions a year.[1] Survival after intensive care have increased during the last decades, and concomitantly it has become apparent that long-term impairments leading to disability after ICU admission are common.[2] The impairments encompass physical, cognitive and mental health problems. All of these impairments hold potential to affect function in society as before arrest, and in working age survivors, the ability to work may be compromised.[3–5]

The chance of a successful outcome following critical illness relies on a complex interplay between pre-existing patient related factors, the type and character of the illness itself, the individual host response to the given illness and the resulting degree of organ dysfunction, which has previously been illustrated by the PIRO-model(predisposition, insult, response, organ dysfunction).[6] In turn each of these four domains of the model, as well as their interplay resulting in the individual course of critical illness, hold ability to result in or affect the emergence and severity of impairments and hereby affect long-term outcomes.

Within a heterogeneous severely ill population, OHCA patients constitutes a relatively homogeneous group. The OHCA-insult is characterized by a sudden circulatory arrest, and hypoxic brain injury a feared adverse outcome. The pathophysiological process leading to this is relatively well described as is the impact of early resuscitative interventions reducing both mortality[7,8] and long-term impairments.[9,10] Nevertheless in OHCA the relation between pre-hospital interventions and the course of the following illness affecting critical care and hospital resource utilization is largely unknown. Further, for both OHCA and general ICU-patients the impact of in-hospital factors on potential long-term impairments remains unclear.

The aim of this thesis was therefore to address the impact of prehospital risk factors and interventions on hospital LOS and proportion of ICU admission in OHCA patients and to address the impact of severity of illness on return to work, maintenance of work and income after ICU admission in both OHCA- and general ICU-patients of working age, working before ICU-admission.

## 1.2 Epidemiology and Critical illness

### 1.2.1 Introduction to intensive care

Intensive care is a relatively new speciality. The idea of caring for the severely injured in a separate unit is dated back to the Crimean war in the1850s and expanded during world war II[11], and the first intensive care department using positive pressure ventilation is dated back to Denmark in 1953.[12,13] Since then, intensive care have evolved and expanded extensively following the understanding of pathophysiology of several organ dysfunctions and the concomitant development of supportive technology.[11] Intensive care is now a central part of the health care system, offering observation as well as organ support treatment for all patients suffering critical illness with risk of or an existing organ failure.[14] Treatment and observation in an ICU is still, as in the 1950's, resource and cost extensive, as both staffing, observational equipment, and technology-level is high.

### 1.2.2 ICU patients

As modern ICUs receive patients from all clinical specialties, the ICU-population is a case mix of a wide range of medical and surgical patients in need of observation and/or treatment in an ICU.[14] Cause of admission may be either acute or elective, and some patients are only admitted shortly for routine observation as for example after major elective surgery. Additionally, duration and criteria for similar ICU admissions may vary with hospital size, region, countries, capacity, patient population and over time due to changes in guidelines. Therefore, no common characteristics describe ICU patients, but rather an existing need of observation or treatment in the ICU as well as a potential reversibility of the condition.[14] Consequently, ICU-patients constitute a markedly heterogeneous population. Survival after treatment in the intensive care have increased during the last decades.[15,16] This increase occurred concurrent with increased resource utilization in the ICU and increased rates of discharge to rehabilitation facilities[15,17] With the growing population of ICU-survivors and the increased need of rehabilitation, it has become apparent that ICU care comes at a cost, both for the individual patient and society.[18]

### 1.2.3 Out-of-hospital cardiac arrest

Cardiac arrest is defined by abrupt interruption of the heart's electrical function, compromising the pump function and hereby circulation to vital organs. Clinically, it is diagnosed by loss of consciousness and absence of normal breathing.[19] Cardiac arrest is not a disease in itself, but rather a symptom of an underlying critical illness and a part of all deaths. Due to the geographical placement, OHCA is, compared to the majority of in-hospital cardiac arrest, typically not preceded by any severe deterioration of health. OHCA will therefore often be the first symptom of severe illness, although approximately every fourth OHCA is preceded by symptoms or disease. Emergency medical services(EMS)-witnessed arrests is in this context a special group where all patients had some sort of preceding condition or complaint that lead to the EMS activation. Therefore, these patients are likely similar to patients with in-hospital cardiac arrest, hence they constitute a population different from other OHCAs with optimal condition for a successful resuscitation attempt.[20]

Incidence of and outcome after OHCA varies between countries, and in Denmark approximately 3,500 patients experience OHCA a year.[7] The main cause of OHCA is an underlying cardiovascular disease and other causes include pulmonary disease, drowning, trauma etc.[21,22] The 'Chain of survival' visualizes the important steps for successful resuscitation and consist of early: 1.Recognition and call for help, 2. Cardio pulmonary resuscitation (CPR) and 3. Defibrillation[23] 4. Advanced life support and post-resuscitation-care.[24] In Denmark, survival has more than doubled in recent years.[25] This increase has been attributed to several national initiatives including mandatory CPR courses when acquiring a driver's license and in elementary schools, increases in physician-equipped mobile response units dispatched to OHCA emergencies, dispatch-assisted guidance in OHCA recognition and dispatch-assisted CPR and widespread dissemination of automatic external defibrillators (AED) in combination increased voluntary CPR courses and media attention directed towards increasing public awareness and knowledge on how-to.[7,26] Similar improvements following national initiatives have also been seen in other countries.[27–31] The improved pre-hospital handling of OHCA have, in addition to increasing survival, been related to functional favourable outcomes, showing that these improvements go beyond survival.[9,10,29,32–34]

The fourth link in the chain of survival consists of advanced life support and post-arrest care. Despite common appreciation of these elements as central and important following OHCA, their impact on outcome is not as established as for the early interventions, and conflicting results exists for instance on the impact of therapeutic hypothermia.[35,36] Advanced life support includes identification and correction of reversible causes, airway handling, delivery of drugs and treatment of arrhythmias as well as monitoring.[37] These efforts continue into post-arrest care, and a large proportion of OHCA patients who survive to hospital admission are admitted to an ICU, and OHCA admissions constitutes approximately 6% of all ICU admissions.[38] Optimal post arrest care as well as transfer to critical care have been associated to improved short-term outcomes.[39–43] The post arrest syndrome is well described and its severity the result of a combination of the cause of arrest, the comorbidity burden and prehospital factors such as duration and severity of arrest.[44] Among survivors to hospital admission, cardiovascular death accounts for majority of deaths during the first three days, whereafter ischemic brain injury is the largest contributor to mortality.[44] The main focus of post-arrest care is therefore to prevent or minimize existing brain injury. Central elements of ICU-post-arrest care include sedation, targeted temperature management, hemodynamic optimization, oxygen, seizure and blood glucose control.[45] Moreover an important purpose of post arrest care is the allowance of sufficient time for neurological prognostication as well as increased focus on examination of rehabilitation needs.[24]

In the light of the heterogeneous ICU-population, ICU-patients with OHCA constitutes a small, but well-defined subpopulation of ICU-patients. Prehospital events, leading to hospital admission and necessitating ICU treatment are relatively well known, and this knowledge and relative heterogeneity of the population enables establishment of a link between pre-admission events and characteristics of the subsequent hospitalization. As the brain is the organ most sensitive to the ischemia caused by abruption of circulation, the leading cause of ICU-admission among OHCA patients is unconsciousness or decreased neurological functioning followed by circulatory instability.[46,47]

### 1.2.4 Organ support treatment in the ICU

Despite the heterogeneity of the ICU-population, a potential or manifest organ-failure is a common denominator.[48] Examples of organ failures are failure of lungs, brain, heart, kidney, liver and coagulation[48], and the most common support modalities are mechanical ventilation, inotropes/vasopressors and renal replacement therapy (RRT).[49]

In observational studies, it is important to bear in mind that the absence of registered organ support therapies may not be the same as the absence of organ failure requiring support.[50] Threshold for both ICU-admission and the administration of organ support may vary with both type of illness and the underlying health of the individual patient and is in addition based on whether the treatment is considered futile. For instance clinicians would tend to withhold supportive therapy for a patient with severe organ failure and an underlying health condition (e.g. metastatic cancer or terminal Chronic obstructive pulmonary disease (COPD) making return to a normal life improbable[6], and even with a more favourable prognosis the threshold for benefit of RRT and cardiovascular support is often debated for different patient categories.[51,52] Hence, in observational studies, the presence and absence of organ support can therefore not always be considered a direct measure of organ failure or need of treatment in the ICU.[50]

The incidence of treatment therapies vary between studies, probably due to differences in case-mix. However, the incidence of mechanical ventilation is consistently high, with frequencies ranging from 53.7-65%.[53] For cardiovascular support therapies frequencies range from 33%[54] -80%[53] and RRT is less commonly used, with incidence reported to range from approximately 10-13% in general ICU-patients [53,55,56] The treatment modalities described are often used in combination[57], e.g. 80% of patients treated with RRT are reported to be concomitantly treated with both cardiovascular support and mechanical ventilation.[58] Incidence of organ support therapy increase with increasing length of ICU stay.[55,59,60]

### 1.2.5 ICU Severity scores

For general ICU-patients, several scoring systems to predict mortality include measures of degree and number of organ affection exists. Examples of scores commonly used are the ‘acute physiology and chronic health evaluation’ (APACHE), SAPS and ‘sequential organ failure assessment score’ (SOFA).[61–63]

The latest revised edition of the APACHE score, APACHE IV, is based on three parts 1.physiological parameters, 2. Age of the patient, 3. Chronic diseases, and includes overall 129 variables.[64] Physiological parameters include i.e. consciousness, heart rate, mean arterial blood pressure, respiratory rate, pH and Creatinine gathered in the first 24 hour of the ICU stay, and chronic diseases include liver cirrhosis, heart failure, Chronic obstructive pulmonary disease and chronic renal failure requiring dialysis, human immunodeficiency virus infection and haematological malignancies.[65] The APACHE is very accurate in predicting ICU-survival, however on a practical level it needs a significant amount of time for data entry and its use is hereby rather time-consuming.[66]

In the data used in this thesis, the SAPS II was available. The SAPS II uses the worst values of 17 variables measured within the first 24 hours of ICU-admission and includes age, temperature, type of admission, systolic blood pressure, heart rate, Glasgow coma scale, White blood cell count, Urine output, blood urea nitrogen, potassium, bilirubin, sodium and bicarbonate level, arterial oxygen concentration, AIDS, metastatic cancer and hematologic malignancy. Hence compared to APACHE the SAPS score needs less data entry and has further been validated in several countries.[64] As for the APACHE score the SAPS score is very accurate in predicting ICU mortality.[64,67]

As a last example of a common predictive tool of ICU mortality, the SOFA score is commonly used. Even though the score was originally designed to assess severity of organ failure in sepsis patients,[68] the highest, mean and an increasing score has been shown to predict mortality in general ICU patients.[69] The score is based on measurements of organ failure (respiratory, cardiovascular, hepatic, coagulation, neurologic and renal) at 24 hours after ICU admission and repeated every 48 hours hereafter.[64]

Despite the overall predictive accuracy of all of the described scores their performance vary with patient population including patients with acute kidney injury, patients on extra corporal membrane oxygenation and cardiac arrest.[64] The variation may reflect that different clinical symptoms, biomarkers and organ affections represent slightly different prognosis across different patient categories. Moreover, in patients admitted more than 10 days to the ICU, severity of illness recorded in the first 24 hours after admission is no longer associated with in-hospital mortality.[70]

The scores described above all include measures of organ dysfunction, and several studies have explored the impact of organ failure on prognosis of the critically ill. However only few and conflicting reports on the relation between organ failure and long-term functional outcomes exists.[4,5] Both the need of mechanical ventilation, need of RRT as well as longer duration of these types of organ support therapies have been shown to reduce survival chances, however knowledge of this impact across patient categories does not exist.[55,56,71] Further organ failure during ICU admission have in previous studies failed to predict long-term survival[70,72] and acute kidney failure have been shown not be associated with health-related quality of life.[73–75]

### 1.2.6 Prognosis after critical illness

Knowledge of both the short- and long-term prognosis of critical illness is important, both to guide clinical decision-making, to understand the impact of different symptoms/events and to inform the patient and relatives. The PIRO-model illustrates the very complex interplay between pre-existing, insult-related and host response related factors resulting in a degree of organ dysfunction.[6] This model also applies for the OHCA patients, however for this patient group prehospital events may have a relatively large impact on outcome compared to the general ICU population. The ICU scoring systems described above also includes various elements from each of the domains of the PIRO model and are important in the prediction of the short term prognosis, in particular short term mortality.

However, with the growing ICU survival and recognition of the fact that a large proportion of ICU survivors experience various combinations and severity of physical, cognitive and mental health impairments, following ICU admission the prediction of a favourable long-term outcome have become increasingly important.[2,76–78]

Impairments following ICU admission and their epidemiology has been described as an entity and termed 'Post intensive care syndrome' (PICS).[79] As for mortality, risk factors for development of PICS can be categorized into pre-existing and ICU-related factors, and vary dependent on whether cognitive, physical or psychiatric sequelae are studied.[80] Examples of major pre-existing risk factors are pre-existing cognitive deficits and a history of psychiatric disease.[81] Examples of ICU-related risk factors are delirium[82,83], prolonged mechanical ventilation[84], renal replacement therapy[85] as well as presence of Acute respiratory distress syndrome (ARDS)[86], and sepsis.[87] OHCA patients are probably at risk of PICS due the ischaemic nature of sequelae holding potential to influence especially cognitive functions, however the impact of in-hospital therapy in this category remains largely unknown.

### 1.2.7 Long-term functional outcomes of critical illness

In 2001 The World Health Organization (WHO) performed a conceptual framework for categorization of physical, cognitive and mental health outcome-measures into impairments in structure and function, activity limitation and participation in social roles.[88] The framework has been used to measure disability following a wide range of severe illnesses,[89] and using this classification in studies of outcomes after critical illness is recommended to facilitate comparisons between different publications.

As the PIRO model, this framework also illustrates the complex interplay between the patient, the illness and the treatment, however the primary focus of this framework is the resulting potential disability rather than survival. First, the pre-admission health of the patient affects impairments following critical illness. If the patient suffers from chronical illness or has an aggressive cancer, this might affect the future impairments, beyond both the injuries caused by a cardiac arrest and events in critical care.[2] Still, organ failure and hereby critical illness may in itself cause physical impairments. Impairments that may lead to activity limitations, which in turn may lead to restriction of participation in social roles. Limitations in activity and participation is as a common notation termed disabilities. Disabilities in combination with the perception of these disabilities affect quality of life. Hence pre-hospital status, severity and type of illness, potential impairments and the ability to handle these impairments are all separate but dependent aspects of the response to critical illness. However, these aspects accumulate to a level of disability.[2]

Often structural or physical impairments are routinely quantified by physicians during an ICU and hospital stay and examples of this are measures of forced expiratory volume in one second (FEV1), 6-minutes-walk test, cardiac ejection fraction and neurological assessment. Further the prevalence of such impairments following critical illness have been quantified in several studies.[90] In turn, these physical impairments may or may not cause limitations in abilities and the link between physical impairments and limitations is not always one-to-one but rather heterogeneous. Limitations are defined by impairments found in tests in a standardized environment and examples of such tests are tests of cognitive executive function such as mini Mental state Examination[91], swallowing test, up and go tests and the heterogeneity of the linkage to physical impairments is illustrated by the fact that similar brain injuries detected on a CT-scan may lead to various results in the mini Mental state Examination.[2]

Disability is, according to the framework, defined by restriction in participation in social roles, and is an interplay between structural impairments, limitations and the individual patient in combination with the social and technological environment of the patient. Inability to work is a common measure of disability, or correspondingly, return to work is a common measure of preserved function following an event, as is performing activities of daily living.[2] Return to work has been assessed among several subgroups of survivors after several types of severe illness, for instance cancer[92], stroke[93] and trauma.[94,9518]

Lastly, as an addition to the WHO framework, it is recommended to include or relate the study of long term outcomes to the health related quality of life.[2,89] This measure assesses the 'relative desirability of measured or estimated health status', and hereby includes the preference of the patient in the measurement of outcome. Health related quality of life is typically assessed by Short Form 36 (SF-36), a questionnaire of 36 questions where the patient can rate their physical and mental health status.[96]

Several scales and indexes combined several aspects from the framework when measuring functional outcomes. As examples of this are: the WHO's Disability assessment schedule was developed (WHODAS 2.0) that assesses disability across six major life domains[97], and the Health utility index[98], taking cognitive and physical functioning as well as emotional status into account.

In conclusion the framework produced by the WHO serves as a tool to understand sequelae after critical illness as a sequential process. Return to work is a measure of the capability to participate and function in society as before an event, and when interpreting this measure it is important to understand that an acquired incapability to work emerge through a complex interplay. The papers of this thesis explored small pieces of this large and complex process.

### 1.2.8 Study design in critical illness

In randomised trials the random allocation of patients minimize risk of bias by equal distributions of confounders and measurement error among study participants receiving and not receiving the treatment respectively.[99,100] Therefore randomized trials or reviews of randomized trials are often considered golden standard of evidence. However, this may primarily be true for the testing of an effect of an intervention. Still, not all interventions can be tested by randomization as for instance random allocation of prehospital interventions in OHCA as well as randomizing delivery of organ-support to patients with manifest organ failure would not be considered ethical. Further, the randomised design do have limitations and last for studies of prognosis, reviews or cohort studies may be preferred.[100]

As the ICU-population is very heterogeneous, equal distribution of confounders would necessitate a very large study population. This could be handled by restricting the study population to a smaller subpopulation with fewer confounders, however this could limit generalizability of such a study. Even with these obstacles overcome selection bias may also occur due to of differential loss to follow-up among intervention groups even in a large scale randomized trial.[101] Differential loss to follow up may be a problem especially when a long duration of follow up is necessary. Therefore a randomized study of long-term outcomes following ICU-admission even with a large sample size may not be generalizable, even though the internal validity may be high.[102]

Therefore, when aiming at representing an unrestricted sample of ICU patients, cohort studies may be preferred and may even have additional advantages compared to randomised prospective designs, in particular when studying return to work. However, in cohort studies, cautious handling of confounders and interpretation of data as well as carefulness regarding conclusions about causality are important. When designing a cohort study, it is important to take into account sources of selection and information bias as well as confounding and addition consider the possibility of chance. Hereby we minimize the risk possibly erroneous conclusions of causality. However if such sources of bias are properly accounted for, and despite the fact that bias and chance may still exist and arise from unmeasured or residual confounding, cohort studies are valuable in the study of in particular prognosis of the critically ill.

## 1.3 Background and existing literature

### 1.3.1 Pre-hospital risk factors for ICU-admission following OHCA

Prevention of long-term disability begins with the prevention of critical illness.[2] Therefore, it is important to investigate how different efforts reduce risk of organ failure and minimize risk of complications to avoid or reduce long-term disability.[103]

Risk factors for ICU-admission in general and following OHCA are not extensively studied. Therefore we reviewed the literature for evidence on risk factors for ICU admission following both OHCA and in general.

### 1.3.2 Existing literature

For OHCA patients, Petrie et al found in a study of health care costs[104] that 61% of 113 survivors to ward- or ICU-admission, were admitted to an ICU, however they did not identify risk factors for ICU admission.[105] In a similar Dutch study of health care costs Van Alem et al found that early defibrillation reduced health care costs due to reduced length of ICU stay.[106] This study did not explore risk factors for ICU-admission, and did not report exact rate of ICU-admission, however approximately 90% of the 144 patients were admitted to an ICU.[106]

Early predictors of ICU-admission are studied in many different settings and patient populations, and predictors of ICU-admission in one population may not apply to another. Still, across different study-populations age, comorbidities and markers of severity of illness tend to recur as factors with an impact on the risk of ICU admission. As such in 43.000 Acute myelogenous leukaemia-patients age below 80 years, increasing number of comorbidities and presence of infection predicted ICU-admission.[107] Among patients admitted with a dengue infection, patients admitted to an ICU were older and more often had diabetes. For these patients the combination of early markers (e.g. hypotension, organ affection, low platelet count) indicating severe illness, predicted ICU-admission.[108] In addition comorbidities as well as increasing age was risk factors for ICU-admission across different patient populations.[109,110]

In conclusion, sparse amounts of evidence suggest that delayed initiation of relevant treatment is related to increased risk of ICU admission in OHCA. General factors with an impact on the risk of ICU admission are age, burden of comorbidities as well as markers of severe illness. Hence, the relation between pre-hospital interventions and the subsequent hospitalization remains sparsely studied.

### 1.3.3 Return to work following OHCA

Long-term patient centred outcomes following OHCA are important, [111] and with the improved survival to hospital admission, the prognostic value of the in-hospital course have become increasingly important. Anoxic brain damage is common and feared following OHCA[112], hence evaluation of outcome following OHCA focus on the presence and the functional impact of such an injury with potential to result in both physical and mental impairments. Physical impairments following OHCA are mainly neurological which is often measured by the Cerebral Performance score (CPC) and the modified Rankin scale (mRs) often in addition to the measuring instruments described above.[111,113] Common mental sequelae following OHCA are anxiety, depression[114] and are important to recognize and possibly treat.

Severe organ dysfunction following OHCA, may to some extent reflect the ischaemic injury caused by the arrest. Return to work is a proxy for regaining life as before arrest and thereby an indicator for a favourable neurological outcome. Further, capability to return to work following severe organ dysfunction and support, indicates that the damage was transient rather than permanent, and that the OHCA in itself and the following hospital course did not affect the mental health of the patient to a degree that limited the patient in resumption of work.

### 1.3.4 Existing literature

Literature with return to work after OHCA as primary outcome is sparse and its relation to the in-hospital course, is to our knowledge, not previously studied. We performed a literature search with the terms: (("Out-of-Hospital Cardiac Arrest"[Mesh]) AND ("Employment"[Mesh] OR "Return to Work"[Mesh])), which only returned the two relevant studies summarized in the top of table in table 1. By inspection of references of these articles, we identified 8 relevant articles.

In a recent cohort study of return to work among 796 Danish 30-day OHCA survivors, demographic, socioeconomic and prehospital associated factors was explored. 76% survivors were employed after 2 years and lower age, higher education, higher income, arrest 2006-2011 vs 2005-2005, as well as bystander CPR and bystander defibrillation was associated with increased chance of return to work. Furthermore, 30-day survivors who returned to work, stayed in the work force for a median of 3 years and maintained salary at a pre-arrest level.[9]

Similarly an earlier smaller Danish study of return to work, among comatose OHCA survivors treated with targeted temperature management, 65% of patients working pre arrest, returned to work[32], and in addition previous studies reported similar rates.[115–117]

Contrarily lower rates of return to work following OHCA has also been reported. In an early Swedish study 40 (42%) of 95 survivors working prior to arrest returned to work[119], and in another study out of 14 employed survivors only 4 (29 %) returned to work. Moreover, in a German study only 7 out of 17 survivors employed prior to arrest returned to work.[121]

| Author, publication year, [ref] | Country | N (Working) | Design | Patients | Setting, study period | Follow-up Outcome | Result |
|---|---|---|---|---|---|---|---|
| Primary outcome: | | | | | | | |
| **Kragholm, 2015**[9] | Denmark | 796 | Cohort | OHCA | 2001-2012 | Return to work | 76,6 % returned to work |
| **Kragholm, 2013**[32] | Denmark | 87 | Cohort | Comatose OHCA patients treated with hypothermia | 2004-2009 | Return to work | 65% returned to work |
| Secondary outcome: | | | | | | | |
| **Fugate JE, 2013**[118] | USA | 38 | Cohort | OHCA, treated with hypothermia | 2006-2011 | 20 months, Cognition | 79% returned to work |
| **Graves JR, 1997**[119] | Sweden | 95 | Cohort | OHCA-survivors | 1980-93 | 36 mths, CPC,mortality | 42% returned to work |
| **Hofgren C, 1984**[120] | Sweden | 14 | Cohort | OHCA survivors | - | 2 years, Cognition | 29% returned to work |
| **Bergner L, 1984**[116] | Sweden | 206 | Cohort, questionnaire | OHCA survivors | - | 6 months | 78% returned to work, 51% of full time |
| **Sunnerhagen KS, 1996**[121] | Germany | 17 | Cohort questionnaire | Cohort, questionnaire | 1990-1991 | 26 months | 41% returned to work |
| **Tresch DD, 1984**[117] | USA | 32 | | OHCA survivors after Bypass | 1974-82 | 56 months | 72% returned to work |

Table 1. Literature with return to work following OHCA as primary or secondary outcome

### 1.3.5 Return to work following intensive care

The emergence of PICS and increased survival among patients admitted to ICU suggest a need to study long term patient-centred outcomes with focus on determinants and modifiable predictors of poor functional outcomes. In line with this, several scientific societies have recommended focus on long-term patient-centred outcomes following ICU-admission.[122] In recent years, long-term outcomes following intensive care have been extensively studied.[18]
No consensus or golden standard exists with regard to long-term outcome assessment of ICU survivors.[18,122] As in OHCA patients, return to work after ICU and hospital discharge may reflect an ability to participate and function [1819]in society as before hospitalization with critical illness, and it is as such an important outcome from both a patient and societal perspective.

### 1.3.6 Existing literature

We identified studies exploring employment outcomes following ICU admission, with the following search:

("Employment"[Mesh] OR "Return to work"[Mesh]) AND ("Intensive Care Units"[Mesh] OR "Critical illness"[Mesh]) NOT "Workplace"[Mesh] which gave 96 hits. By title and abstract review we found x studies to be of interest and these are summarized in table 2.

Overall, studies on return to work following ICU-admission show divergent results. Four studies measured return to work among general ICU-survivors and found that return to work ranges from 50-78% after 1-2 years[3,124–126] An early study of ARDS patients treated with extracorporeal membrane oxygenation (ECMO) showed a very low proportion of patients who returned to work (26%)[127], however a recent large study of 346 survivors working prior to ICU admission only 44% were jobless one year after ARDS, and that lower severity of illness measured by a modified sequential SOFA score was associated with increased chance of return to work ( OR 2.4 95% CI: 1.12-5.0).[4] In patients with severe sepsis admitted to an ICU, 60% of 42 patients returned to work[128] and in ICU-admitted trauma patients return to work also diverged, ranging from 34 to 57% after 1 year. [129–131]

Lastly, a recent Australian multicentre study studied the impact of disability among ICU survivors. Based on WHO's disability assessment schedule they assessed return to work in 107 patients working prior to admission. After 6 months 60% had not returned to work due to disabilities. Predictors of disability were

anxiety/depression, divorce, longer duration of mechanical ventilation, and this disability was associated with not returning to work.[89]

Small study populations were a common limitation of all studies of return to work after critical illness. In addition all studies were follow up studies with great problems of loss to follow up, which may have biased the results.

| Author, year [ref] | Country | N | Design | Patients | Setting, study period | Follow-up outcome | Result |
|---|---|---|---|---|---|---|---|
| **Hodgson,2017**[8] [9] | Australia | 107 | Cohort | Mechanically ventilated | | 6 months | 40% returned |
| **Kamdar,2017**[4] | USA | 346 | Cohort | ARDS | | 12 months | 44% Jobless |
| **Kamdar, 2017**[5] | USA | 67 | cohort | ARDS | 2004-2007 | 1,2,3,4,5 years | 1 yr: 33/67,2 yr: 37/67,3 yr: 43/67,4 yr: 43/65,5 yr:44/64 |
| **Norman, 2016**[124] | USA | 113 | Cohort | Medical/ Surgical | | 12 months | 45% employed, 7% part time, sofa score; OR=2.361.12-5.0 |
| **Zhan, 2013**[128] | China | 42 | Cohort | Sepsis | 2003-2008 | 12 months | 60% employed |
| **Hodgson, 2012**[132] | Australia | 18 | Cohort | ARDS, ECMO | 2009-11 | 8 months | 26% returned to work |
| **Myhren,2010**[3] | Norway | 122/194 | Cohort | ≥ 24 hrs | 2005-2006 | 12 months | 55% returned to work |
| **Ringdal, 2010**[129] | Sweden | 126 | Cohort | Trauma | 2001-2002 | 0.5, 1.5, 5.5 years | 57% 1.5 years, 78% 5.5 years, (included looking for work) |
| **O'Brien, 2009**[133] | Ireland | 24 | Cohort | Overdose | 2004-2006 | 31 months | 7 employed |
| **Livingston, 2009**[134] | USA | 76 | Cohort | Trauma, ICU-LOS >10 days | 2002-2005 | 3.3 years | 49% returned to work |
| **Jackson JC, 2007**[131] | USA | 47 | Cohort | Trauma, IS-score>25 | 2003 | 12-24 months | 34% unemployed(28/47) |
| **Eddleston, 2000**[125] | UK | 47 | Cohort | General ICU | 1995-96 | 12 months | 78% returned to work |
| **Parno, 1984**[126] | | 90 | Cohort | General ICU | | 24 months | 62% returned to work |

Table 2 Literature concerning return to work following ICU admission

# 2 Aims of the thesis

1. To explore prehospital factors associated with hospital length of stay and ICU-admission in out-of-hospital cardiac arrest.

2. To explore the association between organ-support treatment in the ICU and return to work in out-of-hospital cardiac arrest.

3. To explore the association between organs support treatment in the ICU and return to work in a general ICU population.

We hypothesized that return to work would be low following ICU-admission, both for OHCA survivors and the general ICU-population and that it would decrease with increasing degree of organs supported in both patient populations. Furthermore it was our hypothesis that patients with prehospital interventions had a reduced hospital LOS and reduced need of intensive care, probably due to reduced morbidity.

# 3 Methods

## 3.1 Study design and setting

In all three studies of this thesis, a register-based nationwide cohort design was used. In Denmark, all citizens are at birth given a civil registration number, which enables linkage between registries and ensures a high degree of follow-up.

In the first two studies we studied survivors after OHCA. For this we used the Danish cardiac arrest registry, as the Danish EMS personnel in all five regions of Denmark here have reported every incidence of OHCA since June 1st 2001 as described in detail in both study 1 and 2 of this thesis.

In the first two studies we also used information on whether patients were admitted to an ICU and in study three identified our study cohort among patients admitted to an ICU. Since 2005, The Danish Intensive Care Database, a quality Database established to monitor quality of the intensive care, have obtained data from the Danish national patient registry on date of ICU admission, duration of ICU-LOS and mechanical ventilation, and from 2011 information on SAPS II score. The Danish Intensive care Database have collected and validated data from all admissions to an ICU. Therefore, as described by the Danish Intensive Care Database we identified all ICU-admissions using the Danish procedure codes NABE/NABB.[1]

## 3.2 Data sources

### 3.2.1 The Danish National Patient Registry

For all three studies we used data from Danish National Patient Registry containing information on all hospital admissions since 1977, and since 20015 codes for ICU admission and procedures concerning this.[135] The registry contains admission and discharge dates, information on type of admission (emergency room, outpatient or inpatient), procedure codes, codes added to procedures, a primary admission diagnosis and secondary diagnosis, which in the study period was classified according to the International classification of diseases (ICD) 10th revision. In all three studies we used information from this registry to quantify pre-existing comorbidities, identify ICU-admission and calculate hospital LOS by combining consecutive admissions including transfers between departments, allowing a maximum of 1 day between these admissions. In study three we further used information on primary admission diagnosis for the hospital contact and type of admission (acute/elective surgical or non-surgical) from this registry.

### 3.2.2 The Danish Civil Personal Registration Registry

In all three studies, we used information from the Danish Civil Personal Registration Registry.[136] The Civil Personal Registration System holds, on a daily basis, information on migration and vital status for each Danish citizen. Additionally this registry assigns the unique civil registration number to each Danish citizen either at birth or migration, enabling linkage between registries.

### 3.2.3 The Danish Cardiac Arrest Registry

For studies 1 and 2 we used data from the Danish Cardiac Arrest Registry. The Danish Cardiac Arrest Registry holds information on all out-of-hospital cardiac arrests in Denmark from June 2001 to December 2014, in which a resuscitation attempt was initiated either by EMS personnel or by bystanders. The registry includes information on date and time of arrest, location of arrest, witness status, cerebral status(awake, not awake, as recorded by the EMS personnel at arrival to the hospital),  initial recorded heart rhythm, whether the patient was defibrillated by EMS, time from call to EMS arrival and bystander cardiopulmonary resuscitation and bystander defibrillation.[7]

### 3.2.4 The Dream registry

For studies 2 and 3, we obtained data on work status and return to work from the DREAM registry[137], a registry administered by the Danish Labour Market Authorities that holds weekly information on all social transfer payments (benefits) since 1991. A citizen is registered as being on social transfer payment when he or she receives one or more days of social benefits within a week. Data from this registry have previously been validated by Hjollund et al, and the positive predictive value of being self-supportive was as high as 98,2%.[137]

### 3.2.5 The Danish Prescription Registry

For study 3 we used information from the Danish prescription registry also known as the 'Register of medicinal Products Statistics'. This registry holds information on all prescriptions dispensed from outpatient pharmacies, with data on CPR, drug according to the Anatomical Therapeutic Chemical (ATC) classification, total prescription dosage and date of sale [138,139] We identified patients with dispenses of antidiabetic drugs, or drugs related to anxiety or depression 180 days prior to hospital admission.

### 3.2.6 Statistics Denmark

For study two and three we obtained Income and status of living alone from Statistics Denmark, where these data are available on a yearly basis, and for study three we obtained these data from statistics Denmark's integrated database for labour market research(IDA).

### 3.2.7 Regional data on duration of ICU-admission

From the electronic patient journal we obtained information on duration of ICU-admission for patients admitted to an ICU department at Aalborg university hospital south in the years 2005-2014 as well as registered codes for ICU duration reported to the Danish national Patient registry.

## 3.3 Study populations, exposure, outcome and confounders

### 3.3.1 Study populations

For study 1 we studied the impact of prehospital interventions on both hospital LOS and proportion of ICU-admissions among OHCA patients. To be able to explore the effect of in particular bystander interventions, we excluded EMS-witnessed arrest as well as OHCAs with a presumed non-cardiac cause of arrest from this study. Further to reduce the influence of early death, among patients who did survive to hospital admission, however with a detrimental prognosis, we included only patients who survived to the first day following OHCA. Similarly for the analysis of hospital LOS we excluded patients who died before hospital discharge. As such a short hospital LOS represented a favourable outcome rather than early death. Lastly for the analysis of ICU admission, we excluded OHCAs from before 2005, as data on ICU admission did not exist prior to this year.

In study two we studied the impact of ICU therapy following OHCA on return to work, and therefore only included OHCAs from 2005 and onwards. As the impact of organ failure is probable to persist across causes for arrest, we contrary to the first study, included both non-cardiac causes of arrest as well as EMS witnessed arrest, however did exclude the latter patients in a sensitivity analysis. As the outcome of interest in this study was return to work, we only included patient 18-65 years of age, who were working prior to arrest. As a last exclusion criteria we excluded all patients treated with dialysis prior to arrest, to ensure that renal replacement therapy represented a part of the post cardiac arrest syndrome.

For study 3, instead of only OHCA patients, we included all patients admitted to an ICU for more than 72 hours in the period 2005-2014. The remaining exclusion criteria were similar to the study on organ support following OHCA, however in this study we did not include any non-ICU patients and to avoid patients only admitted for short routine observation we further excluded patients with missing data on ICU-LOS.

As previously described by using the procedure codes NABE/NABB we identified patients admitted to an intensive care department for all three studies, however only for study three we excluded patient registered with codes for intensive care not registered by non-ICU departments, as defined by the Danish Intensive Care Database. [1401]

### 3.3.2 Exposures

In study 1, the primary exposure were bystander efforts, and because very few patient received bystander defibrillation without CPR we divided patients into three categories. 1. No bystander efforts. 2. Bystander CPR only. 3. Bystander-defibrillation with or without bystander CPR.[141]

For both study 2 and 3 number of organs supported in an ICU after OHCA was our exposure, as were the individual type of organ support. Organ support was defined as organ support during ICU admission after OHCA before day 30.  As SAPS-scores and ICU-LOS further are measures of severity of illness, we explored these as additional exposures in study 3.

### 3.3.3 Outcomes

For study 1 we explored hospital LOS and proportion of ICU admission as proxies for severity of illness following OHCA.

For study 2 return to work was primary outcome, and in this study 2 we defined return to work as the first 2 week span, counting from day 30 after OHCA, in which patients received no social benefits, except from state education fund grants, maternity leave or leave of absence.

Return to work was also the primary outcome for study three, however in contrast to OHCA-survivors, in this study-population more patients had periods of up to 4 weeks of no social benefits before either death or longer periods of social benefits. Therefore to ensure that we did not misinterpret short periods of missing registrations in the DREAM registry as return to work, we only quantified such periods as self-support if they were longer than four weeks.

For study 3 we included maintenance of work defined by duration of time in the work force until a leave of more than 5 weeks. Further, in study three for patients who returned and did not retire or die within the first year after return we compared income in the year before hospital admission with the first two years year following hospital admission, to quantify whether patients were able to maintain salary following ICU-admission. Lastly, for ICU-patients who did not return to work, we quantified social benefits in the year following discharge, and for patients who returned to work but withdrew within the first year after return we quantified social benefits in the first four weeks of withdrawal.

For study 2 and 3 we performed several analysis not included in the papers due to lack of space. We quantified maintenance of work for OHCA patients, and for both OHCA-patients and general ICU-patients who returned to work and did not die or retire in the year following return to work, we calculated the proportion of social benefits during the first year after return to work to quantify the prevalence of both shorter and longer leaves among patients who were able to return to work. This measure was previously used among patients admitted with acute myocardial infarction.[142]

### 3.3.4 Potential Confounding

For all three studies covariates for the models were selected using Directed acyclic graphs (DAGs). This method is a structural approach to the identification of and control of confounding factors. A DAG visualises assumptions and knowledge the author have about the scientific question. Through an underlying mathematical model, sources of confounding leading to systematic bias and potential structural bias arising from the selected statistical model can be identified. A DAG can support the researcher in identifying a minimal sufficient set of adjustment variables and to explore how the existing study design may lead to bias.[143] However, as a DAG is only a visualisation of both existing knowledge, beliefs and the author's subjective perceptions of the research question, it is important to bear in mind that by using DAGS, confounding may still be present. Importantly we can never be sure that all potential confounders are included and even in the case of knowledge on all confounders, a DAG is still subjected to subjective interpretation of the included factors and their mutual relations in the present research question.

The concepts of selection bias, information bias and confounding can be visualised and understood through DAGs.[144] Arrows indicates causal directions and if we for instance know that prehospital health affect the clinical decision of ICU-admission, we should add an arrow from prehospital health to ICU-admission. In DAG-theory a path is defined as an unbroken sequence of arrows that do not pass through the same variable more than once, and can be both causal and non-causal. The expression 'backdoor path' covers that another path, than the direct path from exposure to outcome exist, and if not blocked will lead to bias. This is illustrated in the figure below.

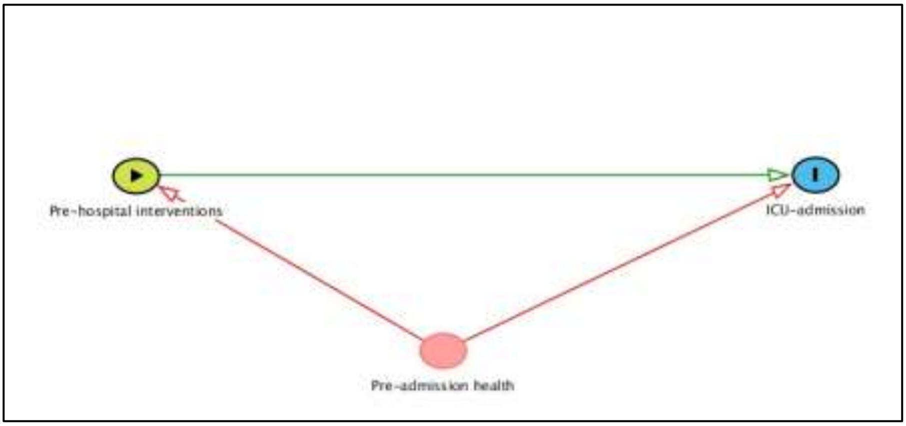


Figure 1. The green circle illustrates exposure, the blue circle the outcome. The green arrow represents the research question and the red circle and red arrows a backdoor path and hereby a source of confounding of the research question.

Selection bias is a systematic error that occurs when the association between exposure and outcome is different in the selected cohort compared to the general population. In DAG terminology, selection bias is structurally defined, as an open backdoor path that occurs, when study participation is conditioned on a common effect of exposure and outcome or a cause of these.[145] Selection bias may occur due to baseline selection, loss to follow up and also missing data.

Information bias is a bias that arise if a non-random measurement error or misclassification is dependent on the outcome or the exposure, also termed ‘dependent differential misclassification’. Several sources of information bias exist, if we for instance use proxy variables, these may not reflect the variable we are actually interested in, as for instance organ support as a proxy for organ failure, and in addition variables are often measured with error. For continuous variables information bias is often referred to as measurement error, and for categorical variables misclassification.

Confounding is defined by a systematic bias that arises when we have a variable that is related to both the exposure and the outcome but not a link in the causal relation. However, in the theory behind causal diagrams, not all confounders lead to confounding in a given study. Therefore, in DAG terminology, the concept of confounding is preferred over a confounder. Structurally, in DAGs, confounding arises when exposure and outcome shares a common cause.[145] In the acyclic graph this lead to an open backdoor path as illustrated above and hereby an association between exposure and outcome which is not caused by a causal relation. If such an open backdoor exist, we can close it by conditioning on this common cause in our model. Examples of conditioning are randomization, adjusting in a multivariate model, matching, stratification etc.

For study 1 we identified by literature review of common confounders for outcome following OHCA as well as risk factors for ICU admission in general age[146], sex[147], comorbid conditions[147], witness status[9] and time interval between recognition of arrest and EMS arrival[148], as well as year of arrest[7] as potential confounders, and included these in our statistical models. However in this study unmeasured confounding may still occur, for instance do we not have information on whether clinicians refrained from intensive therapy despite unconsciousness, the quality of CPR and duration of intensive care or mechanical ventilation.

For study 2, age, sex, educational background, comorbidities, calendar year of arrest and status of living alone were identified as confounders for the association with return to work.[9] Additionally we included witness status, bystander CPR and bystander defibrillation in a separate model. These may be confounders, however it is also possible that organ support to some extent mediates the effect of these prehospital factors. To explore whether this is this case, an analysis of mediation is necessary. However, due to the existence of several both in-hospital and prehospital factors that could influence this process, mediation analysis was not considered feasible and without the scope of the research question.

For study 3, age, sex[53], educational background[9], comorbidities[54], calendar year of admission, whether patients lived alone[9], pre-existing anxiety and depression[89] and cause of admission were identified as confounders. However, as age, comorbidities and type of admission are included in calculation of the SAPS score these factors were not included in the regression model of associations between SAPS scores and return to work.

## 3.4 Statistical analysis

In all three studies normally distributed continuous variables were reported using means and standard deviation and else medians and 25-75 percentiles. We present categorical variables with percentages and frequencies. Trends in temporal changes in continuous outcomes was analyzed using linear regression and for categorical the Cochrane-Armitage trend test.

### 3.4.1 Cumulative incidence (study I, II and III)

We used the Aalen-Johansen estimator to depict the cumulative incidence of discharge alive and in-hospital mortality in study 1. In study 2 three we depicted return to work with death as competing risk for 30 day survivors after OHCA and 90-day survivors after ICU admission. In both studies we depicted maintenance of work, also with death as competing risk, for patients who returned to work. The cumulative incidence does per see not take covariates into account, and due to different distributions of confounders among exposure-groups the adjusted relative risk of being in one group compared to another may change when confounders are included.

### 3.4.2 Regression models

Inclusion of confounders are possible in regression models, and regression models are in general the relationship between a dependent variable and a set of independent explanatory variables plus unexplained random variation. In this thesis we have used linear regression for linear outcomes, logistic regression for dichotomous outcomes and Cox regression for time-to-event outcomes.

Linear regression is based on some assumptions. In univariable and multivariable linear regression analysis, in study 1, we examined the association between bystander interventions and log-transformed hospital LOS. As data was collected from the nationwide Danish Patient Registry, the unexplained random variation deviations was considered independent, as systematic reporting bias of duration of admission is unlikely.The assumption of linearity was assessed using QQ-plots, and the model was checked by diagnostic plots of the residuals where no systematic trend in variation occurred. Assumptions were met when hospital LOS was log-transformed.

Also in study 1, we analyzed associations between prehospital factors and proportion of ICU admission using univariate and multivariate logistic regression. Logistic regression is used to model binary outcome returning an odds ratio. A logistic regression is also based on assumptions. As in linear regression, all observations should be independent. For each observation only two possible [127]outcomes must exist and that log of odds is a linear function on included continuous variables.

In study 2 and 3 we used the Cox proportional hazard model to assess hazard ratio of time to return to work for number of organs supported, combinations of organ support and individual types of organ support. We adjusted for confounders by multivariate Cox regression.

The Cox regression model is a semiparametric model and therefore it makes no assumption about the underlying rate. However, the model assumes that censoring occurs independent given the covariates of the model. In general the model can be used to describe the association between exposure and time to the event of interest.

Assumption of proportional hazards can be checked in many ways: log-log plots, Schönfield- and Martingale residuals. There is no consensus on best way to check the proportional hazards assumption.[149]

For the exposure and selected confounders, we tested the assumption of proportional hazards by log-log plot and Martingale residuals to ensure that the hazard ratio did not change extensively over the time period. When assumptions were not adequately met for covariates and no interaction was found for the covariate in question, the analysis was stratified in the model on these variables.

### 3.4.3 Interaction/effect modification

Interaction is a statistical term, denoting a situation where the influence of two variables on a third is not additive, as an example illustrated by that the effect of duration of a circulatory arrest on hospital length of stay would differ among men and women illustrated by a different slope on the linear relation for these two groups. Interaction is often considered in regression analysis, where inclusion of interaction terms improve the predictive value of the model. However, in clinical questions the impact of a significant interaction term is often hard to interpret, and the clinical relevant question is often whether the effect of an exposure differs significantly across subgroups, often termed biological interaction or effect modification. This can be tested by comparison of estimates across subgroups. In the first study of this thesis we primarily tested for statistical interaction, however in both study two and three we included several stratified analysis to examine a possible effect modification of the impact of organ support across subgroups.

### 3.4.4 Sensitivity analyses

Sensitivity analysis are performed to test the robustness of a model. In study 2 we performed a number of sensitivity analyses: we excluded patients with EMS-witnessed arrests and patients not awake at arrival to hospital to explore whether the associations between organ support and return to work was consistent for these populations.

### 3.4.5 Missing data and multiple imputation methods

In observational studies, missing data is almost unavoidable, and if data is not missing completely at random, complete case analysis may yield biased estimates. As such, the risk of bias depends on the mechanism leading to missingness[150] Multiple imputation is a method that, based on the distribution in the observed data, creates multiple copies of the dataset, in which missing values are replaced by imputed values. In our studies we created between 50 copies, which in imputation is suggested as more than sufficient and enough to reduce the variability created by the imputation process.[150] For each of these datasets the regression model is fitted, and estimates from the combined model take uncertainty of the missing values into account.[150] Multiple imputation is one of many methods to deal with missing data and is based on the assumption that data is missing completely at random or missing at missing at random.[150] Data can be presumed to be missing at random, if we have information on all covariates predictive of missing data and if so, all these variables should be included in our imputation model. In all three studies of this thesis we used multiple imputation to estimate values of missing variables in our regression models, and presumed that data was missing at random. The assumptions was checked by inspection of missing data patterns and by inspection of plausible mechanism behind missing data, which did not lead us to suspect informative missing. For multiple imputation we used the substantive Model Compatibly Fully Conditional Specification multiple Imputation which is a relatively new approach ensuring that each covariate in a model with missing data is imputed based on a model appropriate for this variable(e.g. linear regression for continuous variables, logistic for binary and so on.) taking the substantive model as well as distributions of remaining variables into account.[151]

#### 3.4.6 Ethics

It is not necessary to obtain ethical approval for register based studies, but before execution, we reported all studies to the Danish Data protection Agency study 1:(2007-58-0015, internal reference GEH-2014-017/I-Suite no. 02735). Study 2: 2007-58-0015, internal reference GEH-2014-017/I-Suite no. 02735). Study 3 Agency (2015-57-0002, internal reference 2016-051-000001 / Suite no. 432):

# 4 Results

## 4.1 Study 1

Study 1 included 6,519 OHCA patients, not witnessed by the EMS, ≥ 18 years old, with a presumed cardiac etiology to arrest, of whom 4,641 survived to day 1 after OHCA. 2,545 survived to hospital discharge. Among the 1-day survivors, we excluded 658 patients hospitalized before 2005 for the analysis of ICU admission leaving 3,983 patients for this analysis.[141]

### 4.1.1 Hospital LOS

Among discharge survivors, we found that hospital length of stay differed significantly among bystander categories. For patients who did not receive bystander interventions, median length of stay was 20 days [Q1-Q3: 13-37], median length of stay was 16 days [Q1-Q3: 10-28] for patients who received only bystander CPR, and 13 days [Q1-Q3: 8-20] for patients defibrillated by bystanders. To ensure that this finding was not influenced by differential death before hospital discharge, we depicted the cumulative incidence of being discharged alive, categorized by bystander efforts with death before discharge as a competing risk. Mortality was highest among patients who did not receive bystander interventions and lowest for those with CPR and defibrillation, concomitantly median time to death during hospital admission did not differ among bystander effort categories.

In adjusted linear regression, bystander CPR and bystander defibrillation were associated with a reduction in hospital length of stay among patients surviving to hospital discharge.

### 4.1.2 ICU admission

Among the 3.983 patients who survived to day one after OHCA between 2005 and 2014, 3.047(76.5%) of these were admitted to an ICU, and the proportion increased during the study period. from 71.8% in 2005 to 80.0 % in 2014 (P-trend 0.017).

In both univariable and multivariable logistic regression-models, bystander CPR and bystander defibrillation were associated with lower risk of admission to ICU.

## 4.2 Study 2

Among 33,789 patients who experienced an OHCA 2005-2014, 1,087 survived to day 30, were employed prior to OHCA and of age 18-65 years. (Study 2)

Among patients treated with organ support, most patients (n=494) received two types of organ support, and the majority of these (n=488) received mechanical ventilation in combination with cardiovascular support. These organ support therapies were also the most common organ support therapies in patients receiving one type of organ support, 142 (67.0 %) received mechanical ventilation and 34(16.0%) cardiovascular support. Overall, 33 patients received RRT and of these, 26 patients received all three types of organ support.

Overall 80.5% [95% CI: 78.1-82.9%] returned to work in a two-year follow-up period, and 3.1% [95% CI: 2.1-4.2%] died. In patients not treated in the ICU return to work was 88.5% [95% CI: 85.1-91.8] and decreased with increasing number of organs supported to 59.8% [95% CI 49.5-70.1] for patients with support of 3 organs.

In multivariable Cox regression analysis we only included ICU-patients, and compared to patients with support of 0-1 organs patients with support of three organs had decreased chance off return to work, and these results were consistent across adjustment level and when excluding EMS-witnessed cases and patients awake at hospital arrival.

We performed three multivariable Cox regression analyses of the association between the individual types of organ support and return to work. In these models, when compared to ICU-patients without support of the organ in question, patients with both cardiovascular support and RRT were associated with reduced chance of return to work HR 0.65 [95% CI: 0.51-0.82] and 0.38 [95% CI: 0.23-0.65], respectively. Mechanical ventilation was not associated with reduced chance of return to work.

In analyses not included in the paper due to limited space, we assessed maintenance of work for 893 patients who returned to work. When allowing for sick leaves of up to 4 weeks, 50% had withdrawn from work within a 5-year follow-up period. Maintenance of work did not differ across number of organ support.

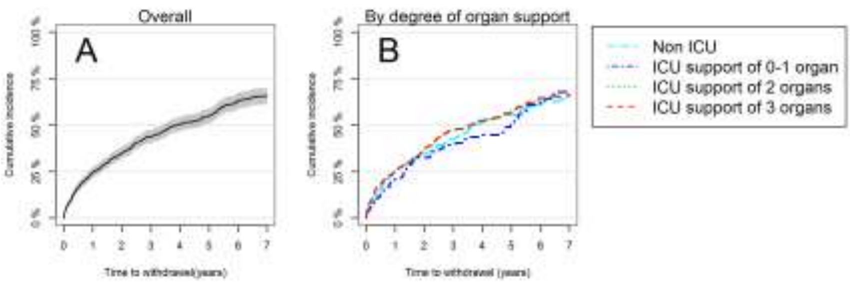


Figure 2 Detachment from work among OHCA patients who returned to work

We calculated a ‘Work participation score’ for 832 patients who returned to work and who did not permanently retire or die within a year after return to work. This score was high with a median work participation of 100% [95% CI: 98-100], and the score did not differ across the number of organs supported (P=0.36). Distribution of the ‘Work participation score’ is shown in figure 3.

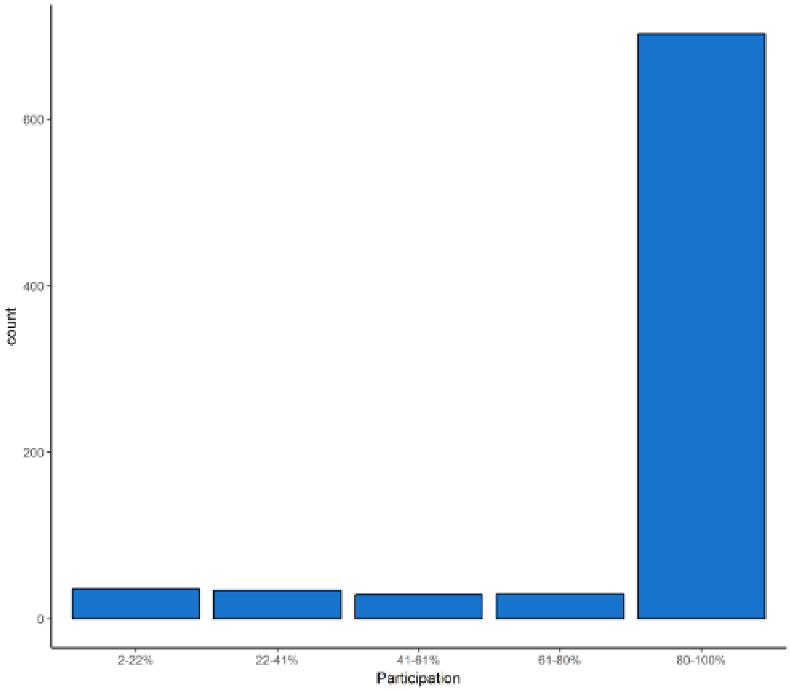


Figure 3, Distribution of work participation among OHCA patients who returned to work and did not retire or die within the first year after return.

### 4.3 Study 3

We included 5,762 ICU-survivors to hospital discharge between January 1 2005 and December 31 2014, who were treated in the ICU for ≥ 72 hours and who were working prior to hospitalization. We excluded all patients with an ICU-LOS below 72 hours as well as patients with missing data on ICU-LOS. ICU-departments receive economic compensation if patients are admitted ≥ 72 hours hence it is likely that patients with missing data on ICU-LOS have an ICU-LOS below 72 hours. However this assumption has not previously been validated. We therefore compared regional data for 18,153 ICU-patients admitted 2005-14 at Aalborg University hospital with codes for ICU-duration reported to the Danish national Patient registry. Of these 5,543 patients did not have a code registered for duration of ICU admission and of these 5,187(93.6%) had an ICU-LOS below 72 hours.

For return to work, median follow-up was 6.38 years, during which 4,274 patients returned to work. When taking death as competing risk into account, the cumulative incidence of return to work was 60.0% (95% CI [58.7-61.3]) 1 year after discharge and 68.0% (95% CI [66.8-69.2]) after two years.

The one- and two-year mortality was 2.93% (95% CI [2.49-3.37]) and 4.24% (95% CI [3.72-4.77]). The chance of return to work differed with type of admission, primary admission diagnosis and need for organ support, and did not change over the study period (article III, Figure 2, Figures 4 -5).

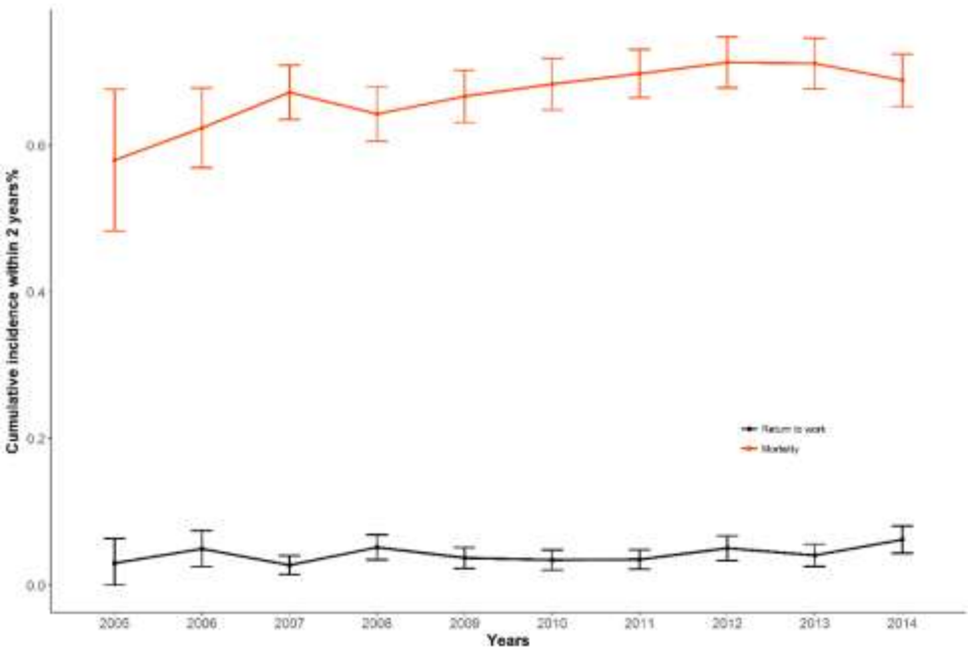


Figure 4 Cumulative incidence of return to work and mortality measured 2 years after hospital discharge by year of ICU-admission.

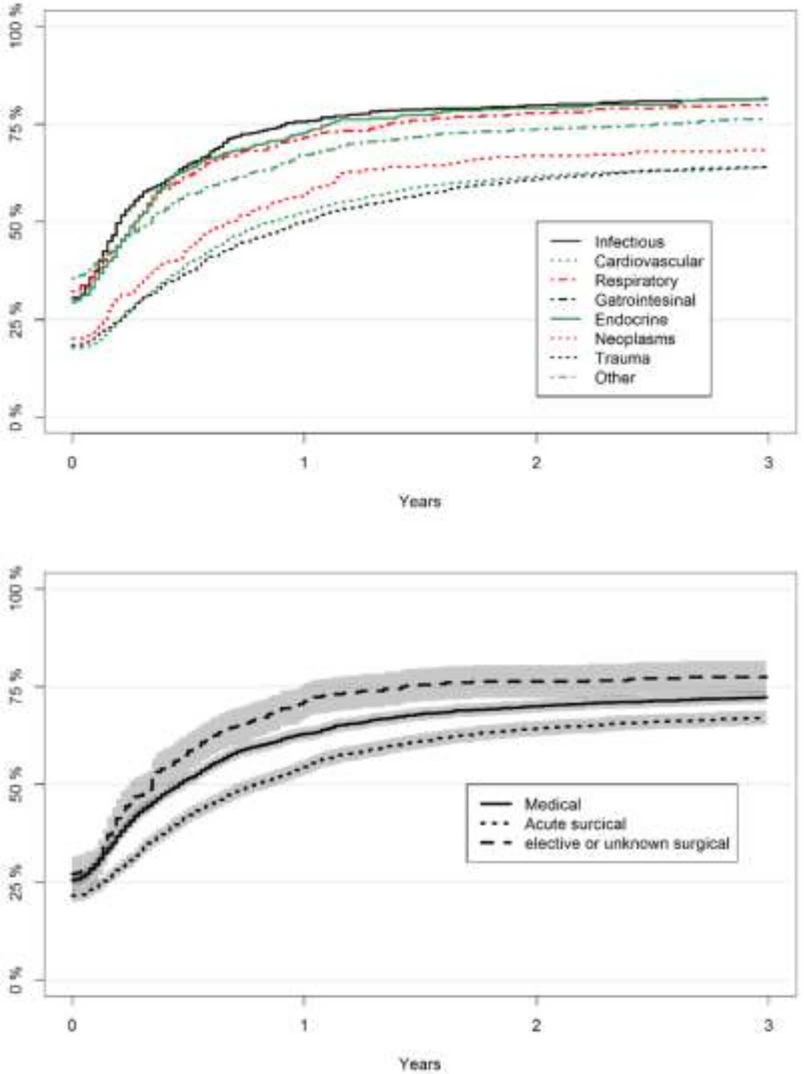


Figure 5. Cumulative incidence of return to work by type of admission and primary admission diagnosis

To assess how long the hospital and ICU discharge survivors stayed in the workforce, we depicted withdrawal from work for 4,274 patients who returned to work. Median time to withdrawal was 3.3 years and median follow up was 5.27(95% CI: 5.08-5.46]) years. 1,235 patients had withdrawn within one year after initial return(Paper 3 figure 2).

The median 'Work participation score' among 3,911 patients who returned to work and who did not retire or die within the first year of return was 100% [25-75%: 86.5-100]), and 2878 (74%) did not receive any social benefits. The distribution of 'work participation' by type of admission and number of organs supported is shown in figure x. When comparing work participation across groups of number of organ support therapies the score was highest for patients with support of 0 organs, (p=0.01) and across admission type the work participation was lowest for acute surgical patients and highest for elective surgical patients (p<0.001).

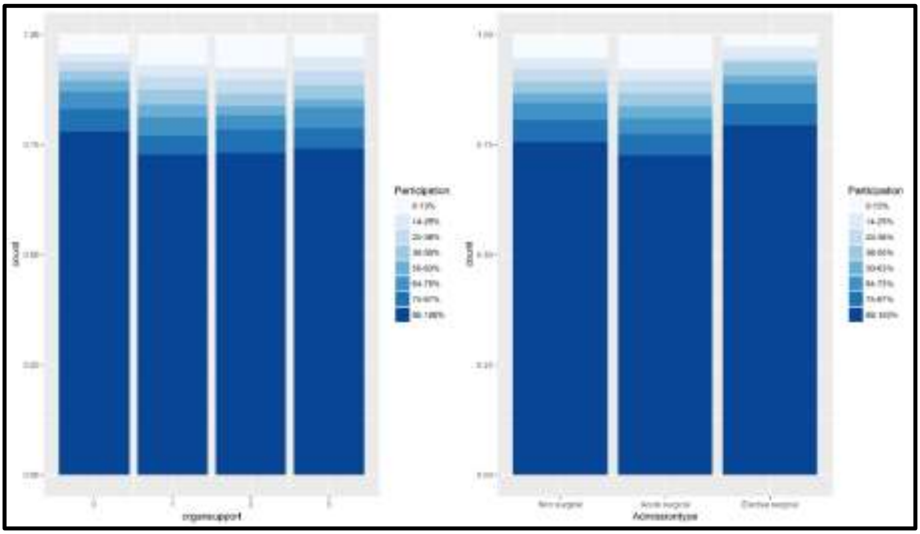

Figure 6, Work participation for general ICU patients who returned to work and did not retire or die within the first year after returning to work. Left: By number of organ support therapies. Right: by type of admission.

For the same group of patients we compared yearly income in the year before ICU-admission with the first and second year following ICU-admission and for both years income decreased with: -1,820 USD (95% CI [-2907:-726], p=0.001) and -1,902 USD (95% CI [-3136:-670], p=0.003), respectively.

The social benefits during the first year after hospital discharge for 1,095 patients who never returned to work and who did not die within 1-year following hospital discharge are shown in table 3. and show that 89% primarily received disability benefits, including sickness benefit, flex job benefits (a social benefit for patients on early retirement pension) and early retirement pension, and that the proportion of permanent disability benefits increased among benefits disbursed for disability. Likewise, the most commonly received social benefits during the first four week span of withdrawal during the first year after return is shown in table x. For these patients, unemployment accounted for 28% and sickness leave for 59% of the social benefits.

| | **Never returned to work (n=1,095)** | | **Returned to work But withdrew within one year after return (n=1,235)** |
|---|---|---|---|
| Age, median[25%-75%] | 47.5 [38.1, 54.1] | | 48.9 [35.3, 57.6] |
| **Unemployment:** | **Social benefits after 1 year** | **Social benefits after 2 years** | |
| Unemployment compensation* | 58 (5.3) | 50(4.6) | 347 (28.1) |
| **Disability:** | | | |
| Sickness benefit* | 710 (65.3) | 315(29.1) | 592 (47.9) |
| Flexible job** | 24 (2.2) | 206(19.0) | 43 (3.5) |
| Early retirement benefit** | 246 (22.6) | 454(41.9) | 92(7.4) |
| Overall disability: | 980(89.5) | 975(89.0) | 727(59.0) |
| **Retirement:** | | | |
| Early retirement** | 17 (1.6) | 22(2.0) | 96(7.8) |
| State pension** | 11(1.0) | 13(1.2) | 15(1.2) |
| Overall retirement: | 28(2.6) | 35(3.2) | 111(9.0) |
| **Other:** | | | |
| Emigrated or missing data* | 29 (2.6) | 35(3.2) | 50 (4.0) |

Table 3, Social benefits for patients who did not return to work during follow up and for patients who withdrew within the first year after return.

In multivariable Cox regression with support of 0 organs as the reference group, we found that support of 1,2 and 3 organs was associated with reduced chance of return to work (HR 0.74 [95% CI [0.68-0.80]), HR 0.79 [95% CI [0.73-0.85]) and HR 0.77 [95% CI [0.67-0.87], respectively. Other factors associated with reduced chance of return to work were acute surgical admission vs non-surgical and living alone vs not living alone. Contrarily, factors associated with higher chance of return to work were: Elective surgery, high education, increasing calendar year and diabetes (figure 6).

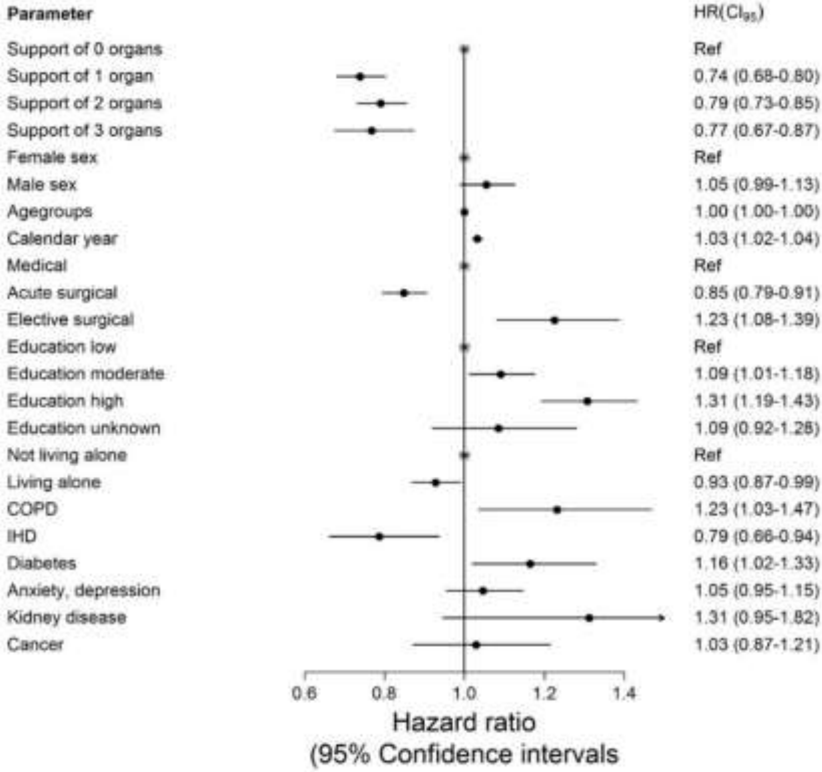


Figure 6, Multivariable Cox regression of return to work. COPD=Chronic obstructive pulmonary disease. IHD: Ischaemic heart disease.

We stratified the adjusted Cox regression analyses of return to work by degree of organ-support by type of admission and by primary admission diagnosis for the hospital contact. Only for patients admitted primarily due to infection we found a significant dose response relationship between return to work and degree of organ support, with lower chances of return to work for patients with increasing number of organ support therapies.

In addition to the number of organs supported we explored the associations between all combinations of organ support as well as the impact of the individual types of organ support and return to work, again in multivariable Cox regression analyses with no organ support as the reference group. In the first analysis, all treatment combinations including mechanical ventilation was associated with a reduced chance of return to work. This was not the case for treatment regimens not including mechanical ventilation. This association was confirmed in the analysis of associations between individual types of organ support treatment and return to work. (Figure 3.1-2, paper 3).

Lastly, we explored whether higher SAPS II scores and length of ICU stay predicted delays in return to work. In 4,399 patients admitted after 2010, we performed adjusted Cox regression models of SAPS II scores and ICU LOS with and without multiple imputation of missing values. Increasing ICU-LOS but not SAPS predicted decreasing chance of return to work. The imputed analyses did not differ from the complete case analysis (Paper 3, figure 4).

# 5 Discussion

## 5.1 Main study findings

This thesis had several main findings. In the first study we found that prehospital interventions reduced both rate of ICU-admission as well as hospital LOS in OHCA patients, indicating that benefits of prehospital interventions do not come at the expense of hospital resources. In the second study we found patients not admitted to an ICU had the highest chance of returning to work and that an increasing need of in-hospital organ support in patients admitted to an ICU following OHCA were predictive of reduced capability to return to work. In the third study we explored whether this finding also applied to a large nationwide cohort of general ICU-patients surviving to hospital discharge with an ICU-stay of more than 72 hours. However, for these patients, mechanical ventilation but not an increasing degree of organ support was associated with decreased chance of return to work. Moreover, the early severity score SAPS II did not predict the chance of returning to work, whereas an increasing ICU-LOS was significantly associated with a decreased chance of returning to work.

In addition we studied various measures of maintenance of work and found that OHCA patients who returned to work stayed in the work force for a long time, and majority of patients did not have a substantial burden of sick leaves. Similarly, the majority of general ICU patients who returned to work were also not substantially burdened by sick leaves. Nevertheless a third of ICU-patients who returned to work became detached from work for more than four weeks within one year after returning, and in addition the majority of these patients and patients who never returned to work became dependent on disability pension benefits. Lastly general ICU patients who returned to work and who did not retire or die within the first year of return, were not able to maintain salary as before ICU-admission.

## 5.2 Predictors of ICU admission and hospital LOS (Study 1)

Our study was the first to examine associations between pre-hospital interventions and hospital LOS and proportions of ICU-admissions following OHCA. Generally there are limited data on determinants of such outcomes among OHCA-patients, nevertheless both our findings of length of stay and ICU-admission confirmed the results from a Dutch study of health care costs related to OHCA, where patients defibrillated more rapidly had a decreased length of ICU stay.[106]

For a possible causal explanation of our findings, our results can be compared to experimental animal studies, where data from dogs indicated that insufficient delivery of oxygen and the duration of this was associated with multi-organ failure.[152] If early interventions reduce degree of ischaemic tissue injury, decreasing the severity of the post-arrest syndrome and hereby reduced degree organ damage, this may be part of the causal explanation of the reduction in hospital LOS and need of life support in an ICU.

## 5.3 Return to work (Study 2 and 3)

Among all OHCA-survivors, we found that 80 % returned to work within two years. This proportion was slightly higher than in previous Danish studies of OHCA patients.[9,32] The small difference is likely explained by inclusion of different time periods or patient-populations. We studied data from 2005-2014, whereas the study from 2015 included patients from 2001-2011. In this study return to work increased over time, with a proportion of 77.6% returning to work during 2006-2011, thus comparable to our findings. The Danish study from 2013 only included ICU-patients treated with hypothermia, which is very likely to explain the lower rate of return to work of 65 % in this study. Contrarily in an American cohort of OHCA survivors treated with therapeutic hypothermia, this number was as high as 79% and hereby similar to return to work rates in our study.[115] However, only 73% of survivors were interviewed, which may have led to selection bias, if only patients with the best outcomes attended.

In our study of the general cohort of ICU survivors, return to work was lower than for the OHCA patients as 60 % and 68 % returned to work within one and two years respectively. Nevertheless this rate of return to work placed itself in line with the only two earlier studies of return to work among general ICU patients.[3,125] Our study was the first to examine return to work following general ICU-admission in a nationwide scale, and extends previous study by size of study population, no loss to follow up and practically complete data on employment.

## 5.4 Predictors of return to work (Paper 2 and 3)

In both study 1 and 2 organ support therapy was associated with reduced chance of return to work, which to our knowledge has not previously been demonstrated. As the chance of return to work decreased with an increasing number of organ support therapies for OHCA patients, this was not the case for the general cohort of ICU-patients. However, for the subgroup of patients admitted with infectious diseases as primary diagnosis for the hospital contact, we found a clear dose-response association between increasing degree of organ support and decreasing degree of return to work. Previous studies of organ support and long term outcomes are sparse, and in addition conflicting, as mechanical ventilation and its duration but not acute kidney injury is with poor long-term outcomes.[73,744,55] That an increasing need of organ support do not hold potential to affect long-term outcomes is rather contra intuitive. However, our findings indicate that both our results and the conflicting literature may stem from differences in case mix, and that organ failure may be an important predictor of long term outcome in at least OHCA and infectious diseases.

In our study SAPS II was not associated with return to work, which is in line with a previous study of ARDS survivors.[5] Furthermore, such measures of severity of illness also including APACHE and SOFA apart from SAPS II are not predictive of long-term survival in previous studies.[7072] As for the impact of organ support, this finding is rather surprising, although it may be explained by a very high mortality for severely ill patients, so that patients with a high SAPS who survive are a highly selected population.[75] As a very significant predictor of reduced chance of return to work, we identified longer ICU-LOS. ICU-LOS reflect several aspects of the hospitalization. For instance patients with worse prehospital health, severe illness, complications and difficulties in weaning from mechanical ventilation would tend to have longer ICU-LOS, and hereby ICU-LOS reflects the complex sum of several factors all with a potential to impact long term impairments. As such the relation between prehospital intervention and hospital LOS found in study 1 illustrates part of this complex interplay for OHCA patients.

## 5.5 Maintenance of work (Study 2 and 3)

For OHCA patients, median time to withdrawal was 5 years which was in line with the one previous study exploring this measure.[9] For the general cohort, median time to withdrawal was lower than for OHCA patients. However reported proportion of sick leaves, part time jobs and new unemployment have previously been reported to be high in a small cohort of ICU-survivors.[153] Further, in a larger questionnaire based study among ARDS survivors, unemployment rates was reported to be 25% at 1 year and 37% after 5 years[5], which is in line with our findings.

Time to any longer leave of absence from work is one measure of maintenance of work, but does not take into account that patients may return again after a period of absence. Furthermore, the measure does not take into account shorter leaves of absence with subsequent return to work. Therefore, for both general ICU patients and OHCA patients who did return to work and who did not retire or die within the first year after return, we explored the total weeks of absence during the first year after return to work. The purpose of this measure was to assess sick leaves as a measure of vulnerability of patients who were able to work following severe illness. This measure have previously been used for cardiac patients, showing recurrent sick laves to be common among these.[154] However, the vast majority of OHCA patients did not have any sick leaves whereas this was more common for general ICU survivors. As such these studies expound on the burden of shorter recurrent sick leaves among this population following return to work and substantiate that general ICU-survivors are a vulnerable population.

## 5.6 Maintenance of income (Study 3)

We observed a significant decrease in income for general ICU-patients, who returned to work, when comparing yearly income in the year before ICU-admission with the first two years after ICU-admission. This has only been investigated in one previous study.[5] However, methods used to obtain income was different from our study. Moreover results may also be affected by structural differences in societies studied. In Denmark we have a public health insurance system, were both the employer and the employee is refunded when an employee is on sick leave. This may have several consequences: Firstly patients may to a large extent be economically compensated in Denmark, hence no difference in income. Secondly, the welfare system, and rules not to fire employees on sick leave, diminishes joblessness and allows for patients to return to work despite a large degree of sick leaves. Despite these advantages we still found a decrease, indicating that even ICU-survivors able to return to work are not able to maintain income.

## 5.7 Distributions of Social benefits (Study 3)

To further explore mechanisms of absence from work, we studied the distributions of social benefits for general ICU-patients who never returned and for patients who returned but withdrew within one year after return. The majority of social benefits that patients received consisted of disability pension and sick leaves, indicating that health issues are leading causes of reduced return to work, withdrawal from work and lost earnings.

## 5.8 Methodological considerations:

Overall, in this PhD-thesis, we sought to establish and explore risk factors for and consequences of in-hospital morbidity in critically ill patients. However, several limitations may exist and may affect or even cause the associations found in studies. These limitations are 1. Selection bias, 2. Information bias, 3. Confounding, 4. Chance, which are all addressed in the sections below.

### 5.8.1 Selection bias

Overall due to the register based design, we had minimal loss to follow up, and furthermore we included all patients with OHCA and all patients admitted to an ICU during our study periods.

Overall in study I on prehospital interventions and ICU admission and length of stay in OHCA, we may have selection bias if registration to the Danish Cardiac Arrest Registry by EMS staff is not complete and if underreporting is systematic. However it is unlikely that there is a systematic underreporting problem that is associated with hospital length of stay and ICU-admission. In study I, for the study of ICU-admission we only included survivors to day 1.  Hereby we may have introduced selection bias, as it is likely that both prehospital interventions and ICU-admission may increase the chance of survival to day 2. However, this restriction may also be a strength, as patients with a detrimental diagnosis at hospital admission will not be offered intensive care. If such patients were included in our analysis they would represent a non-salvageable population and the absence of ICU admission would reflect this rather than a less critically ill patient.

In study 2 on organ support and return to work selection bias may arise through selection of ICU patients. In this study we did not exclude the registrations of ICU-admission registered by non-ICU departments. These admissions account for 5-7% of ICU-admissions, and by including these we may have included less ill patients and hereby overestimated the chances of return to a small extent.

In study 3 we excluded registrations from non-ICU departments, and hereby reduced this source of selection bias. We further excluded all patients with missing data on duration of ICU stay. This may have introduced selection bias, however it has been standard practice not to record codes for the duration of ICU stay for patients with a stay below 72 hours, which we in this thesis validated in 18,153 ICU-patients. As we furthermore excluded all patients with a registered ICU-LOS of less than 72 hrs this bias is likely to be very small. In addition patients with missing data on ICU-LOS had less organ-support and higher rates of return to work and furthermore missing rates on ICU-LOS decreased with calendar time, however overall rates of return to work remained the same. Therefore underreporting of ICU-length of stay is unlikely to differential, but rather related to a running-in period following introduction of the codes for the length of stay, especially for patients with a shorter stay. The study of return to work is by nature restricted to survivors who were employed prior to arrest. Being employed prior to admission is in itself associated to increased health related quality of life compared to non-employed patients, indicating a better prognosis in this group compared to unemployed.[3] Therefore, our findings of predictors of a good prognosis cannot be generalized to non-employed patients and not to other long term functional outcomes.

### 5.8.2 Information bias

In all three studies either exposure or outcome were based on codes from the Danish National patient registry, and non-random misclassification of these would lead to information bias. However the PPV of the coding of intensive care admission, acute dialysis and mechanical ventilation are 95.9% (95% CI: 91.8-98.3), 98.0% (95% CI:91.0-99.8), and 100% (95% CI: 95.1-100), respectively[155], and in shock patients the use of vasopressors/inotropes are validated with a PPV of 88.9((79.6-94.3).[156] In addition several of the diagnosis used to quantify comorbidity are validated with a high PPV[157], and further systematic erroneous registration of ICU/hospital length of stay is unlikely.

In study 1 of ICU-admission and hospital LOS, the selection, of 1-day survivors described above, may actually decrease risk of information bias in this study design. We are interested in ICU admission as a proxy variable for severe organ damage, and by excluding un-salvageable patients who died during the first day after OHCA regardless of ICU-admission we only included 1-day survivors and the subset of these 1-day survivors who were not admitted to an ICU primarily consist of less critically ill patients.

In study 2, our classification of organ failure by the proxy organ support therapy may also have introduced information bias. First, we may have underestimated the degree of organ failure, as we were only able to identify three types of organ failure. Oppositely, one can argue that mechanical ventilation, renal replacement therapy and cardiovascular support constitutes rather common and important types of organ failures, whereas for instance liver failure is rather seldom, whit many different implications. Still, based on the selected types of organ failures, information bias may arise if organ support is not administered with the same threshold for exposed vs unexposed patients. In this case organ support may not reflect the same degree of organ affection, and hereby not have the same predictive value. Nevertheless, under registration of organ support as well as reluctance to initiate treatment would bias our findings toward no difference and we may therefore have underestimated the impact of organ failure on outcomes.

Lastly employment data may be subject to misclassification. However, identifying a patient as working, using the DREAM registry has been validated, and the positive predictive value is as high as 98,2%.[158]

Study 3 share sources of information bias with study 2. In this study the classification of organ failure is supported by the SAPS II scores and the duration of ICU stay. Furthermore, if we were to compare the chosen measures of organ support to a SOFA score, presence of RRT would give 4 points, inotropic agents 2+ points and invasive mechanical ventilation 3+ points, and any score of above 3 is considered a failure.[50]

### 5.8.3 Confounding

Confounding is defined by a systematic bias that arises when we have a variable that is related to both the exposure and the outcome, and not a part of the causal relation. However, as previously described, it is not certain that all confounders lead to confounding.

In our studies we have, based on directed acyclic graphs, included several confounders, however unmeasured or residual confounding may still be present.

In study 1 the relation between prehospital factors and both ICU-admission and hospital length of stay could be confounded by insufficient adjustment for both pre-admission comorbidity as well as age. However, by inclusion of these parameters, our estimates did not change. Unmeasured confounding due to changes in clinical practice over time may also be present, however the associations between bystander efforts and outcomes remained after adjustment for calendar year.

In study 2, several confounders for the association between organ failure and return to work were identified. In this study age and comorbidities were also considered relevant confounders as these both may affect organ failure and its proxy organ support as well as the ability to return to work following a cardiac arrest. However, hazard ratios did not differ before and after adjustment. This is likely explained by a relatively young and not very comorbid population. Several other confounders were identified including status of living alone, educational level, sex and calendar year of arrest, but adjustment for these did still not change our findings. Unmeasured confounding for instance from unmeasured comorbidity and social factor cannot be excluded. The same goes for residual confounding due to insufficient level of adjustment for confounders already included in our analyses (e.g. quality of CPR).

Missing data on prehospital variables may have introduced bias. However, multiple imputation analysis with missing data on prehospital variables did not differ from results based on pooled analysis of imputed datasets. Importantly, our findings were robust and persisted in all analyses and across strata of various variables indicating that the relationship between organ-support and return to work after OHCA is real.

In study 3 several potential confounders exist. First, if threshold of administering organ support therapy differed with variables affecting the ability to return to work, confounding may be present. For the analysis of organ support and duration of ICU-admission we identified age, comorbidity, type of admission, status of living alone, socioeconomic status by educational level and income as such confounders, and our estimates remained after this adjustment. For the analysis of SAPS II, status of living alone, socioeconomic status by educational level and income was considered confounders.

For the analysis of the effect of an increasing number of organ support on outcome, cause of admission may be considered a confounder.

### 5.8.4 Chance

Due to the large sample sizes the majority of our finding are not subject to chance. However in the stratified analysis in study 2 and 3 as well as for the 26 patients with three organs supported this may be taken into consideration. However, the confidence intervals were still rather narrow for these groups, and we therefore consider our findings quite robust given the limitations described above.

# 6 Conclusions

## 6.1 Study 1: ICU admission and hospital LOS following OHCA

We found that bystander CPR and bystander defibrillation were associated with a lower risk of ICU admission as well as a lower hospital LOS among survivors to hospital discharge following OHCA.

## 6.2 Study 2: Organ support and return to work following OHCA

In this study we found that 30-day-survivors admitted to intensive care following OHCA have decreased chance of return to work compared to patients not admitted to an ICU. For ICU-patients return to work decreased with an increasing number of organs supported. Only a small proportion of patients needed both mechanical ventilation, cardiovascular support and RRT and among these more than 50% still returned to work.

## 6.3 Study 3: Return to work following ICU admission

Among ICU survivors to hospital discharge 68% returned to work after 2 years. Mechanical ventilation and longer ICU-LOS was associated with reduced chance of return to work. Patients stayed in the workforce for a median of 3.3 years. Sickness benefits and disability pension accounted for most of social benefits among patients who did not return to work during follow up and patients who withdrew from work within one year after return to work. Finally, among patients who returned to work, annual income levels were significantly lower in the years after ICU discharge versus in the year before ICU admission, indicating lost earnings due to health related problems.

# 7 Perspectives

Overall this thesis adds considerable knowledge to the associations between the different phases of severe illness. The studies included in the thesis contributed with updated knowledge on chances of return to and maintenance of work following ICU-admission for both OHCA and general ICU patients. Furthermore, for both populations, this thesis provided new evidence on how several in-hospital factors differently influenced chances of returning to work, and insight into the impact of prehospital interventions on the in-hospital course following OHCA. These observations can both aid and guide future areas of research and support the process of clinical decision making and information to patients and their relatives.

The assessment of factors with impact on the in-hospital course following OHCA expand the knowledge obtained in previous studies as they have primarily or exclusively focused on the relation between prehospital factors and mortality. As hypothesized, early interventions decreased the hospital LOS as well as ICU admission. It indicates that the increased survival resulting from bystander interventions is rather due to the early interventions in the prehospital setting than the increased use of health care resources. This observation encourages ongoing efforts to improve the prehospital interventions. Also this perspective should be considered in future quantifications of health related cost of OHCA. The mechanisms behind the demonstrated effect of early interventions needs further assessment, as for instance the association between timing and quality of early interventions and risk of ICU-admission.

The impact of organ failure following OHCA on the chance of work resumption found in study two, have not been investigated in previous studies. The findings in study two suggests that the in-hospital course is of importance regardless of prehospital interventions. However, knowledge from this single study cannot be used to guide clinicians in predicting future needs for rehabilitation as a large proportion of patients returned to work despite treated with support of three organs and further very few patients needed this degree of support. More studies are needed to explore the relation between in-hospital factors after OHCA and the impact on both long- and short term outcome. Relevant outcomes to be explored encompass the need of rehabilitation, brain damage and nursing home admission. Additionally, the association between prehospital interventions and resulting organ failure needs investigation to further understand the mechanisms behind organ failure following OHCA.

We hypothesized that an increasing degree of organ support would decrease the chance of return to work for general ICU-survivors as for the OHCA patients. However, this was surprisingly not confirmed. Furthermore, in subgroup analysis, increasing degree of organ support only lowered the chances of return to work among patients admitted primarily due to infection. These result may uncover that different mechanisms behind long term impairments may exist across the very heterogeneous ICU population, which is important to keep in mind in the interpretation of differences and similarities of previous and future studies.

The substantial proportion of patients never returning to or detaching from work and the subsequent prevalence of sickness benefits and disability pensions indicates substantial health problems following ICU admissions. This finding warrants a need to study other long term outcomes and their relation the levels of severity of illness and the therapy offered during the ICU stay. Important future studies include need of rehabilitation, home care and nursing home admission following ICU admission. In this context, elderly ICU patients is an expanding population and criteria for admission and level of care are controversial, changing over time and current clinical decisions are often based on poor levels of evidence.[159] Hence future cohort studies exploring the associations between levels of care, severity of illness long- and short-term outcomes in the elderly ICU population are highly relevant.[160] Still cohort studies cannot account for the selection of patients and therapy, warranting future interventional studies on beneficial levels of care.

Our finding may have also have clinical implications. The substantial long term health burden following ICU admission outlines a need for attention of the sequelae and personal consequences for the individual patient. Currently, this receives great research attention. Based on the our  findings we could suggest regular out-patient hospital visits in specialised ICU out-patients clinics for mechanically ventilated patients with ICU LOS of more than seven days as a way to improve the patients mental and physical convalescence and concurrent prospective qualitative data collection.

# 8 References

1. Christiansen CF, Møller MH, Nielsen H, Christensen S. The Danish Intensive Care Database. *Clin Epidemiol*. 2016;8:525-530. doi:10.2147/CLEP.S99476.

2. Iwashyna TJ, Netzer G. The burdens of survivorship: an approach to thinking about long-term outcomes after critical illness. *Semin Respir Crit Care Med*. 2012;33(4):327-338. doi:10.1055/s-0032-1321982.

3. Myhren H, Ekeberg Ø, Stokland O. Health-related quality of life and return to work after critical illness in general intensive care unit patients: a 1-year follow-up study. *Crit Care Med*. 2010;38(7):1554-1561. doi:10.1097/CCM.0b013e3181e2c8b1.

4. Kamdar BB, Sepulveda KA, Chong A, et al. Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. *Thorax*. September 2017:thoraxjnl-2017-210217. doi:10.1136/thoraxjnl-2017-210217.

5. Kamdar BB, Huang M, Dinglas VD, et al. Joblessness and Lost Earnings after Acute Respiratory Distress Syndrome in a 1-Year National Multicenter Study. *Am J Respir Crit Care Med*. 2017;196(8):1012-1020. doi:10.1164/rccm.201611-2327OC.

6. Marshall JC. The PIRO (predisposition, insult, response, organ dysfunction) model: toward a staging system for acute illness. *Virulence*. 2014;5(1):27-35. doi:10.4161/viru.26908.

7. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA*. 2013;310(13):1377-1384. doi:10.1001/jama.2013.278483.

8. Hasselqvist-Ax I, Riva G, Herlitz J, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. *N Engl J Med*. 2015;372(24):2307-2315. doi:10.1056/NEJMoa1405796.

9. Kragholm K, Wissenberg M, Mortensen RN, et al. Return to Work in Out-of-Hospital Cardiac Arrest Survivors: A Nationwide Register-Based Follow-Up Study. *Circulation*. 2015;131(19):1682-1690. doi:10.1161/CIRCULATIONAHA.114.011366.

10. Kragholm K, Wissenberg M, Mortensen RN, et al. Bystander Efforts and 1-Year Outcomes in Out-of-Hospital Cardiac Arrest. *N Engl J Med*. 2017;376(18):1737-1747. doi:10.1056/NEJMoa1601891.

11. Weil MH, Tang W. From Intensive Care to Critical Care Medicine. *Am J*

*Respir Crit Care Med*. 2011;183(11):1451-1453. doi:10.1164/rccm.201008-1341OE.

12. LASSEN HC. The epidemic of poliomyelitis in Copenhagen, 1952. *Proc R Soc Med*. 1954;47(1):67-71. http://www.ncbi.nlm.nih.gov/pubmed/13134175. Accessed October 1, 2017.

13. Berthelsen PG, Cronqvist M. The first intensive care unit in the world: Copenhagen 1953. *Acta Anaesthesiol Scand*. 2003;47(10):1190-1195. doi:10.1046/j.1399-6576.2003.00256.x.

14. Valentin A, Ferdinande P, Improvement EWG on Q. Recommendations on basic requirements for intensive care units: structural and organizational aspects. *Intensive Care Med*. 2011;37(10):1575-1587. doi:10.1007/s00134-011-2300-7.

15. Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R, J M. Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012. *JAMA*. 2014;311(13):1308. doi:10.1001/jama.2014.2637.

16. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit Care*. 2013;17(2):R81. doi:10.1186/cc12695.

17. Carson SS, Cox CE, Holmes GM, Howard A, Carey TS. The Changing Epidemiology of Mechanical Ventilation: A Population-Based Study. *J Intensive Care Med*. 2006;21(3):173-182. doi:10.1177/0885066605282784.

18. Turnbull AE, Rabiee A, Davis WE, et al. Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications. *Crit Care Med*. 2016;44(7):1267-1277. doi:10.1097/CCM.0000000000001651.

19. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. *Resuscitation*. 2004;63(3):233-249. doi:10.1016/j.resuscitation.2004.09.008.

20. Axelsson C, Claesson A, Engdahl J, et al. Outcome after out-of-hospital cardiac arrest witnessed by EMS: Changes over time and factors of importance for outcome in Sweden. *Resuscitation*. 2012. doi:10.1016/j.resuscitation.2012.01.043.

21. Perkins GD, Handley AJ, Koster RW, et al. European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation*. 2015;95:81-99. doi:10.1016/j.resuscitation.2015.07.015.

22. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest. *Resuscitation*. 2015;96(2015):328-340. doi:10.1016/j.resuscitation.2014.11.002.

23. Nolan J, Soar J, Eikeland H. The chain of survival. *Resuscitation*. 2006;71(3):270-271. doi:10.1016/j.resuscitation.2006.09.001.

24. Nolan JP, Cariou A. Post-resuscitation care: ERC–ESICM guidelines 2015. *Intensive Care Med*. 2015;41(12):2204-2206. doi:10.1007/s00134-015-4094-5.

25. Hansen SMH. Danish cardiac arrest Registry. Out-Of_hospital Cardiac arrest in Denmark. Scientific report 2001-2014. http://genoplivning.dk/wp-content/uploads/2016/05/Rapport-fra-Dansk-Hjertestopregister-2001-2014.pdf.

26. Hansen SM, Hansen CM, Folke F, et al. Bystander Defibrillation for Out-of-Hospital Cardiac Arrest in Public vs Residential Locations. *JAMA Cardiol*. March 2017. doi:10.1001/jamacardio.2017.0008.

27. Chan PS, McNally B, Tang F, Kellermann A, CARES Surveillance Group the CS. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation*. 2014;130(21):1876-1882. doi:10.1161/CIRCULATIONAHA.114.009711.

28. Daya MR, Schmicker RH, Zive DM, et al. Out-of-hospital cardiac arrest survival improving over time: Results from the Resuscitation Outcomes Consortium (ROC). *Resuscitation*. 2015;91:108-115. doi:10.1016/j.resuscitation.2015.02.003.

29. Okubo M, Kiyohara K, Iwami T, Callaway CW, Kitamura T. Nationwide and regional trends in survival from out-of-hospital cardiac arrest in Japan: A 10-year cohort study from 2005 to 2014. *Resuscitation*. 2017;115:120-128. doi:10.1016/j.resuscitation.2017.03.036.

30. Kitamura T, Iwami T, Kawamura T, et al. Nationwide Improvements in Survival From Out-of-Hospital Cardiac Arrest in Japan. *Circulation*. 2012;126(24):2834-2843. doi:10.1161/CIRCULATIONAHA.112.109496.

31. Lund-Kordahl I, Olasveengen TM, Lorem T, Samdal M, Wik L, Sunde K. Improving outcome after out-of-hospital cardiac arrest by strengthening weak links of the local Chain of Survival; quality of advanced life support and post-resuscitation care. *Resuscitation*. 2010;81(4):422-426. doi:10.1016/j.resuscitation.2009.12.020.

32. Kragholm K, Skovmoeller M, Christensen AL, et al. Employment status 1

year after out-of-hospital cardiac arrest in comatose patients treated with therapeutic hypothermia. *Acta Anaesthesiol Scand*. 2013;57(7):936-943. doi:10.1111/aas.12142.

33. Ro YS, Shin S Do, Kitamura T, et al. Temporal trends in out-of-hospital cardiac arrest survival outcomes between two metropolitan communities: Seoul-Osaka resuscitation study. *BMJ Open*. 2015;5(6):e007626. doi:10.1136/bmjopen-2015-007626.

34. Hasselqvist-Ax I, Riva G, Herlitz J, et al. Early Cardiopulmonary Resuscitation in Out-of-Hospital Cardiac Arrest. *N Engl J Med*. 2015;372(24):2307-2315. doi:10.1056/NEJMoa1405796.

35. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. *N Engl J Med*. 2013;369(23):2197-2206. doi:10.1056/NEJMoa1310519.

36. Kirkegaard H, Søreide E, de Haas I, et al. Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest. *JAMA*. 2017;318(4):341. doi:10.1001/jama.2017.8978.

37. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation*. 2015;95:100-147. doi:10.1016/j.resuscitation.2015.07.016.

38. Nolan JP, Laver SR, Welch CA, Harrison DA, Gupta V, Rowan K. Outcome following admission to UK intensive care units after cardiac arrest: a secondary analysis of the ICNARC Case Mix Programme Database. *Anaesthesia*. 2007;62(12):1207-1216. doi:10.1111/j.1365-2044.2007.05232.x.

39. Stub D, Schmicker RH, Anderson ML, et al. Association between hospital post-resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. *Resuscitation*. 2015;92:45-52. doi:10.1016/j.resuscitation.2015.04.015.

40. Matsuyama T, Kiyohara K, Kitamura T, et al. Hospital characteristics and favourable neurological outcome among patients with out-of-hospital cardiac arrest in Osaka, Japan. *Resuscitation*. 2017;110:146-153. doi:10.1016/j.resuscitation.2016.11.009.

41. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73(1):29-39. doi:10.1016/j.resuscitation.2006.08.016.

42. David Gaieski ঙঙ F, Band RA, Abella BS, et al. Early goal-directed

hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation*. 2009;80:418-424. doi:10.1016/j.resuscitation.2008.12.015.

43. Langhelle A, Tyvold SS, Lexow K, Hapnes SA, Sunde K, Steen PA. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation*. 2003;56(3):247-263. http://www.ncbi.nlm.nih.gov/pubmed/12628556. Accessed March 9, 2016.

44. Binks A, Nolan JP. Post-cardiac arrest syndrome. *Minerva Anestesiol*. 2010;76(5):362-368. doi:10.1161/CIRCULATIONAHA.108.190652.

45. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 Suppl 3):S768-86. doi:10.1161/CIRCULATIONAHA.110.971002.

46. Perman SM, Gaieski DF. Neurologic status on presentation to a Heart Attack Centre: A predictor of recovery or more aptly, a predictor of injury? *Resuscitation*. 2014;85(7):851-852. doi:10.1016/j.resuscitation.2014.04.025.

47. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive Care Med*. 2013;39(11):1972-1980. doi:10.1007/s00134-013-3043-4.

48. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. *N Engl J Med*. 2012;367(20):1901-1911. doi:10.1056/NEJMoa1209759.

49. Critical care and the global burden of critical illness in adults. *Lancet*. 2010;376(9749):1339-1346. doi:10.1016/S0140-6736(10)60446-1.

50. de Lange DW, Flaatten H. Preventing persistent organ support in ICU patients. *Acta Anaesthesiol Scand*. 2017;61(5):464-466. doi:10.1111/aas.12879.

51. Gaudry S, Hajage D, Dreyfuss D, Joannidis M, Perner A. Optimal timing of renal replacement therapy in patients with acute kidney injury in the context of sepsis. *Intensive Care Med*. 2017;43(10):1546-1547. doi:10.1007/s00134-017-4856-3.

52. St?r-Jensen H, Sunde K, Olasveengen TM, et al. Bradycardia During Therapeutic Hypothermia Is Associated With Good Neurologic Outcome in Comatose Survivors of Out-of-Hospital Cardiac Arrest*. *Crit Care Med*. 2014;42(11):2401-2408. doi:10.1097/CCM.0000000000000515.

53. Vincent J-L, Marshall JC, Ñamendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. *www.thelancet.com/respiratory*. 2014;2. https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S221326001470061X.pdf?locale=en_US. Accessed October 1, 2017.

54. Sakr Y, Reinhart K, Vincent J-L, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study*. *Crit Care Med*. 2006;34(3):589-597. doi:10.1097/01.CCM.0000201896.45809.E3.

55. Meyhoff TS, Krag M, Hjortrup PB, Perner A, Møller MH, SUP-ICU inception cohort study investigators. Use of life support in acutely admitted ICU patients. An international cohort study. *Acta Anaesthesiol Scand*. 2017;61(5):513-522. doi:10.1111/aas.12878.

56. Nisula S, Kaukonen K-M, Vaara ST, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. *Intensive Care Med*. 2013;39(3):420-428. doi:10.1007/s00134-012-2796-5.

57. de Jong E, van Oers JA, Beishuizen A, et al. Effi cacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. 2016. www.thelancet.com/infection. Accessed October 9, 2017.

58. Uchino S, Bellomo R, Morimatsu H, et al. Continuous renal replacement therapy: A worldwide practice survey. *Intensive Care Med*. 2007;33(9):1563-1570. doi:10.1007/s00134-007-0754-4.

59. Harvey SE, Parrott F, Harrison DA, et al. Trial of the Route of Early Nutritional Support in Critically Ill Adults. *N Engl J Med*. 2014;371(18):1673-1684. doi:10.1056/NEJMoa1409860.

60. Kollind M, Wickbom F, Wilkman E, et al. Shock treatment in a cohort of Scandinavian intensive care units in 2014. *Acta Anaesthesiol Scand*. 2016;60(7):945-957. doi:10.1111/aas.12745.

61. Skrifvars MB, Varghese B, Parr MJ. Survival and outcome prediction using the Apache III and the out-of-hospital cardiac arrest (OHCA) score in patients treated in the intensive care unit (ICU) following out-of-hospital, in-hospital or ICU cardiac arrest. *Resuscitation*. 2012;83(6):728-733. doi:10.1016/j.resuscitation.2011.11.036.

62. Doerr F, Badreldin AM, Heldwein MB, et al. A comparative study of four intensive care outcome prediction models in cardiac surgery patients. *J Cardiothorac Surg*. 2011;6(1):21. doi:10.1186/1749-8090-6-21.

63. Bisbal M, Jouve E, Papazian L, et al. Effectiveness of SAPS III to predict hospital mortality for post-cardiac arrest patients. *Resuscitation*. 2014;85(7):939-944. doi:10.1016/j.resuscitation.2014.03.302.

64. Predictive scoring systems in the intensive care unit - UpToDate. https://www.uptodate.com/contents/predictive-scoring-systems-in-the-intensive-care-unit?source=search_result&search=apache&selectedTitle=1~60. Accessed December 5, 2017.

65. Niewiński G, Starczewska MH, Kański A. Prognozowanie śmiertelności na oddziałach intensywnej terapii na podstawie skali APACHE. *Anestezjol Intens Ter*. 2014;46(1):46-49. doi:10.5603/AIT.2014.0010.

66. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med*. 2006;34(5):1297-1310. doi:10.1097/01.CCM.0000215112.84523.F0.

67. Nassar AP, Mocelin AO, Nunes ALB, et al. Caution when using prognostic models: a prospective comparison of 3 recent prognostic models. *J Crit Care*. 2012;27(4):423.e1-7. doi:10.1016/j.jcrc.2011.08.016.

68. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26(11):1793-1800. http://www.ncbi.nlm.nih.gov/pubmed/9824069. Accessed December 5, 2017.

69. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754-1758. http://www.ncbi.nlm.nih.gov/pubmed/11594901. Accessed December 5, 2017.

70. Iwashyna TJ, Hodgson CL, Pilcher D, et al. Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. *Lancet Respir Med*. 2016;4(7):566-573. doi:10.1016/S2213-2600(16)30098-4.

71. Petäjä L, Vaara S, Liuhanen S, et al. Acute Kidney Injury After Cardiac Surgery by Complete KDIGO Criteria Predicts Increased Mortality. *J Cardiothorac Vasc Anesth*. 2017;31(3):827-836. doi:10.1053/j.jvca.2016.08.026.

72. Mildh H, Pettilä V, Korhonen A-M, et al. Three-year mortality in 30-day

survivors of critical care with acute kidney injury: data from the prospective observational FINNAKI study. *Ann Intensive Care*. 2016;6(1):118. doi:10.1186/s13613-016-0218-5.

73. Villeneuve P-M, Clark EG, Sikora L, Sood MM, Bagshaw SM. Health-related quality-of-life among survivors of acute kidney injury in the intensive care unit: a systematic review. *Intensive Care Med*. 2016;42(2):137-146. doi:10.1007/s00134-015-4151-0.

74. Oeyen S, De Corte W, Benoit D, et al. Long-term quality of life in critically ill patients with acute kidney injury treated with renal replacement therapy: a matched cohort study. *Crit Care*. 2015;19(1):289. doi:10.1186/s13054-015-1004-8.

75. Oeyen S, Vandijck D, Benoit D, Decruyenaere J, Annemans L, Hoste E. Long-term outcome after acute kidney injury in critically-ill patients. *Acta Clin Belg*. 2007;62 Suppl 2:337-340. http://www.ncbi.nlm.nih.gov/pubmed/18283995. Accessed October 18, 2017.

76. Rabiee A, Nikayin S, Hashem MD, et al. Depressive Symptoms After Critical Illness. *Crit Care Med*. 2016;44(9):1744-1753. doi:10.1097/CCM.0000000000001811.

77. Desai S V., Law TJ, Needham DM. Long-term complications of critical care. *Crit Care Med*. 2011;39(2):371-379. doi:10.1097/CCM.0b013e3181fd66e5.

78. Herridge MS, Tansey CM, Matté A, et al. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. *N Engl J Med*. 2011;364(14):1293-1304. doi:10.1056/NEJMoa1011802.

79. Davydow DS, Desai S V., Needham DM, Bienvenu OJ. Psychiatric Morbidity in Survivors of the Acute Respiratory Distress Syndrome: A Systematic Review. *Psychosom Med*. 2008;70(4):512-519. doi:10.1097/PSY.0b013e31816aa0dd.

80. Post-intensive care syndrome (PICS) - UpToDate. https://www.uptodate.com/contents/post-intensive-care-syndrome-pics?source=search_result&search=pics&selectedTitle=1~31. Accessed November 29, 2017.

81. Wunsch H, Christiansen CF, Johansen MB, et al. Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. *JAMA*. 2014;311(11):1133-1142. doi:10.1001/jama.2014.2137.

82. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of

long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. 2010;38(7):1513-1520. doi:10.1097/CCM.0b013e3181e47be1.

83. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369(14):1306-1316. doi:10.1056/NEJMoa1301372.

84. De Jonghe B, Sharshar T, Lefaucheur J-P, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288(22):2859-2867. http://www.ncbi.nlm.nih.gov/pubmed/12472328. Accessed August 29, 2017.

85. Guerra C, Linde-Zwirble WT, Wunsch H. Risk factors for dementia after critical illness in elderly Medicare beneficiaries. *Crit Care*. 2012;16(6):R233. doi:10.1186/cc11901.

86. Herridge MS, Cheung AM, Tansey CM, et al. One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2003;348(8):683-693. doi:10.1056/NEJMoa022450.

87. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794. doi:10.1001/jama.2010.1553.

88. WHO. *Interbational Classification of Functioning, Disabilty and Healt*. Geneva; 2001. http://apps.who.int/iris/bitstream/10665/42407/7/9241545429_tha%2Beng.pdf. Accessed November 9, 2017.

89. Hodgson CL, Udy AA, Bailey M, et al. The impact of disability in survivors of critical illness. *Intensive Care Med*. 2017;43(7):992-1001. doi:10.1007/s00134-017-4830-0.

90. Parry SM, Granger CL, Berney S, et al. Assessment of impairment and activity limitations in the critically ill: a systematic review of measurement instruments and their clinimetric properties. *Intensive Care Med*. 2015;41(5):744-762. doi:10.1007/s00134-015-3672-x.

91. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935. http://www.ncbi.nlm.nih.gov/pubmed/1512391. Accessed November 9, 2017.

92. de Boer AG, Taskila TK, Tamminga SJ, Feuerstein M, Frings-Dresen MH, Verbeek JH. Interventions to enhance return-to-work for cancer patients. In: de Boer AG, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2015:CD007569. doi:10.1002/14651858.CD007569.pub3.

93. Tanaka H, Toyonaga T, Hashimoto H. Functional and occupational characteristics associated with very early return to work after stroke in Japan. *Arch Phys Med Rehabil*. 2011;92(5):743-748. doi:10.1016/j.apmr.2010.12.009.

94. Brenneman FD, Redelmeier DA, Boulanger BR, McLellan BA, Culhane JP. Long-term outcomes in blunt trauma: who goes back to work? *J Trauma*. 1997;42(5):778-781. http://www.ncbi.nlm.nih.gov/pubmed/9191655. Accessed August 10, 2016.

95. Holtslag HR, Post MW, van der Werken C, Lindeman E. Return to work after major trauma. *Clin Rehabil*. 2007;21(4):373-383. doi:10.1177/0269215507072084.

96. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483. http://www.ncbi.nlm.nih.gov/pubmed/1593914. Accessed November 9, 2017.

97. Ustün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ*. 2010;88(11):815-823. doi:10.2471/BLT.09.067231.

98. Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Med Care*. 2002;40(2):113-128. http://www.ncbi.nlm.nih.gov/pubmed/11802084. Accessed November 9, 2017.

99. Juul, Svend; Hammer Bech, Bodil; Dahm, Christina C; Rytter D. *Epidemiologi Og Evidens 3.Edition*.; 2017.

100. OCEBM Levels of Evidence - CEBM. http://www.cebm.net/blog/2016/05/01/ocebm-levels-of-evidence/. Accessed December 5, 2017.

101. Hodgson C, Cuthbertson BH. Improving outcomes after critical illness: harder than we thought! *Intensive Care Med*. 2016;42(11):1772-1774. doi:10.1007/s00134-016-4526-x.

102. Rothman KJ. Six persistent research misconceptions. *J Gen Intern Med*. 2014;29(7):1060-1064. doi:10.1007/s11606-013-2755-z.

103. Li G, Malinchoc M, Cartin-Ceba R, et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. *Am J Respir Crit Care Med*. 2011;183(1):59-66. doi:10.1164/rccm.201003-0436OC.

104. Brummel NE, Jackson JC, Pandharipande PP, et al. Delirium in the ICU and

Subsequent Long-Term Disability Among Survivors of Mechanical Ventilation*. *Crit Care Med*. 2014;42(2):369-377. doi:10.1097/CCM.0b013e3182a645bd.

105. Petrie J, Easton S, Naik V, Lockie C, Brett SJ, Stümpfle R. Hospital costs of out-of-hospital cardiac arrest patients treated in intensive care; a single centre evaluation using the national tariff-based system. *BMJ Open*. 2015;5(4):e005797. doi:10.1136/bmjopen-2014-005797.

106. van Alem AP, Dijkgraaf MGW, Tijssen JGP, Koster RW. Health system costs of out-of-hospital cardiac arrest in relation to time to shock. *Circulation*. 2004;110(14):1967-1973. doi:10.1161/01.CIR.0000143150.13727.19.

107. Halpern AB, Culakova E, Walter RB, Lyman GH. Association of Risk Factors, Mortality, and Care Costs of Adults With Acute Myeloid Leukemia With Admission to the Intensive Care Unit. *JAMA Oncol*. 2017;3(3):374. doi:10.1001/jamaoncol.2016.4858.

108. Pang J, Thein T-L, Leo Y-S, Lye DC. Early clinical and laboratory risk factors of intensive care unit requirement during 2004–2008 dengue epidemics in Singapore: a matched case–control study. *BMC Infect Dis*. 2014;14(1):649. doi:10.1186/s12879-014-0649-2.

109. Morgan DJR, Ho KM, Armstrong J, Baker S. Incidence and risk factors for intensive care unit admission after bariatric surgery: a multicentre population-based cohort study. *Br J Anaesth*. 2015;115(6):873-882. doi:10.1093/bja/aev364.

110. AbdelSalam H, Restrepo C, Tarity TD, Sangster W, Parvizi J. Predictors of Intensive Care Unit Admission After Total Joint Arthroplasty. *J Arthroplasty*. 2012;27(5):720-725. doi:10.1016/j.arth.2011.09.027.

111. Becker LB, Aufderheide TP, Geocadin RG, et al. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. *Circulation*. 2011;124(19):2158-2177. doi:10.1161/CIR.0b013e3182340239.

112. Moulaert VRMP, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: A systematic review. *Resuscitation*. 2009;80(3):297-305. doi:10.1016/j.resuscitation.2008.10.034.

113. Raina KD, Callaway C, Rittenberger JC, Holm MB. Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation*. 2008;79(2):249-256. doi:10.1016/j.resuscitation.2008.06.005.

114. Lilja G, Nilsson G, Nielsen N, et al. Anxiety and depression among out-of-

hospital cardiac arrest survivors. *Resuscitation*. 2015;97:68-75. doi:10.1016/j.resuscitation.2015.09.389.

115. Fugate JE, Moore SA, Knopman DS, et al. Cognitive outcomes of patients undergoing therapeutic hypothermia after cardiac arrest. *Neurology*. 2013;81(1):40-45. doi:10.1212/WNL.0b013e318297ee7e.

116. Bergner L, Bergner M, Hallstrom AP, Eisenberg M, Cobb LA. Health status of survivors of out-of-hospital cardiac arrest six months later. *Am J Public Health*. 1984;74(5):508-510. http://www.ncbi.nlm.nih.gov/pubmed/6711733. Accessed November 6, 2017.

117. Tresch DD, Wetherbee JN, Siegel R, et al. Long-term follow-up of survivors of prehospital sudden cardiac death treated with coronary bypass surgery. *Am Heart J*. 1985;110(6):1139-1145. http://www.ncbi.nlm.nih.gov/pubmed/4072871. Accessed November 6, 2017.

118. Fugate JE, Moore SA, Knopman DS, et al. Cognitive outcomes of patients undergoing therapeutic hypothermia after cardiac arrest. *Neurology*. 2013;81(1):40-45. doi:10.1212/WNL.0b013e318297ee7e.

119. Graves JR, Herlitz J, Bång A, et al. Survivors of out of hospital cardiac arrest: their prognosis, longevity and functional status. *Resuscitation*. 1997;35(2):117-121. http://www.ncbi.nlm.nih.gov/pubmed/9316194. Accessed November 6, 2017.

120. Hofgren C, Lundgren-Nilsson Å, Esbj Rnsson E, Sunnerhagen KS. Two years after cardiac arrest; cognitive status, ADL function and living situation. *Brain Inj*. 2008;22(12):972-978. doi:10.1080/02699050802491289.

121. Sunnerhagen KS, Johansson O, Herlitz J, Grimby G. Life after cardiac arrest; a retrospective study. *Resuscitation*. 1996;31(2):135-140. http://www.ncbi.nlm.nih.gov/pubmed/8733020. Accessed November 6, 2017.

122. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502-509. doi:10.1097/CCM.0b013e318232da75.

123. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med*. 2007;33(11):1876-1891. doi:10.1007/s00134-007-0772-2.

124. Norman BC, Jackson JC, Graves JA, et al. Employment Outcomes After Critical Illness: An Analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors Cohort. *Crit Care Med*. 2016;44(11):2003-2009. doi:10.1097/CCM.0000000000001849.

125. Eddleston JM, White P, Guthrie E. Survival, morbidity, and quality of life after discharge from intensive care. *Crit Care Med*. 2000;28(7):2293-2299. http://www.ncbi.nlm.nih.gov/pubmed/10921555. Accessed October 23, 2017.

126. Parno JR, Teres D, Lemeshow S, Brown RB, Avrunin JS. Two-year outcome of adult intensive care patients. *Med Care*. 1984;22(2):167-176. http://www.ncbi.nlm.nih.gov/pubmed/6700277. Accessed October 25, 2017.

127. Hodgson CL, Hayes K, Everard T, et al. Long-term quality of life in patients with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation for refractory hypoxaemia. *Crit Care*. 2012;16(5):R202. doi:10.1186/cc11811.

128. Zhang K, Mao X, Fang Q, et al. Impaired long-term quality of life in survivors of severe sepsis. *Anaesthesist*. 2013;62(12):995-1002. doi:10.1007/s00101-013-2257-8.

129. Ringdal M, Plos K, Ortenwall P, Bergbom I. Memories and health-related quality of life after intensive care: a follow-up study. *Crit Care Med*. 2010;38(1):38-44. doi:10.1097/CCM.0b013e3181b42909.

130. Livingston DH, Tripp T, Biggs C, Lavery RF. A fate worse than death? Long-term outcome of trauma patients admitted to the surgical intensive care unit. *J Trauma*. 2009;67(2):341-8-9. doi:10.1097/TA.0b013e3181a5cc34.

131. Jackson JC, Obremskey W, Bauer R, et al. Long-term cognitive, emotional, and functional outcomes in trauma intensive care unit survivors without intracranial hemorrhage. *J Trauma*. 2007;62(1):80-88. doi:10.1097/TA.0b013e31802ce9bd.

132. Hodgson CL, Hayes K, Everard T, et al. Long-term quality of life in patients with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation for refractory hypoxaemia. *Crit Care*. 2012;16(5):R202. doi:10.1186/cc11811.

133. O'Brien BP, Murphy D, Conrick-Martin I, Marsh B. The functional outcome and recovery of patients admitted to an intensive care unit following drug overdose: a follow-up study. *Anaesth Intensive Care*. 2009;37(5):802-806. http://www.ncbi.nlm.nih.gov/pubmed/19775045. Accessed October 18, 2017.

134. Livingston DH, Tripp T, Biggs C, Lavery RF. A fate worse than death? Long-term outcome of trauma patients admitted to the surgical intensive care unit. *J Trauma*. 2009;67(2):341-8-9. doi:10.1097/TA.0b013e3181a5cc34.

135. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30-33. doi:10.1177/1403494811401482.

136. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3.

137. Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Public Health*. 2007;35(5):497-502. doi:10.1080/14034940701271882.

138. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38-41. doi:10.1177/1403494810394717.

139. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f. doi:10.1093/ije/dyw213.

140. Summary vital statistics[in Danish]. Statistics Denmark Website. statistikbanken.dk. Accessed March 1, 2017.

141. Riddersholm S, Kragholm K, Mortensen RN, et al. Association of bystander interventions and hospital length of stay and admission to intensive care unit in out-of-hospital cardiac arrest survivors. *Resuscitation*. July 2017. doi:10.1016/j.resuscitation.2017.07.014.

142. Biering K, Hjøllund NH, Lund T. Methods in measuring return to work: a comparison of measures of return to work following treatment of coronary heart disease. *J Occup Rehabil*. 2013;23(3):400-405. doi:10.1007/s10926-012-9405-x.

143. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol*. 2008;8:70. doi:10.1186/1471-2288-8-70.

144. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48. http://www.ncbi.nlm.nih.gov/pubmed/9888278. Accessed December 20, 2016.

145. VanderWeele TJ, Robins JM. Directed Acyclic Graphs, Sufficient Causes, and the Properties of Conditioning on a Common Effect. *Am J Epidemiol*. 2007;166(9):1096-1104. doi:10.1093/aje/kwm179.

146. Wissenberg M, Folke F, Hansen CM, et al. Survival After Out-of-Hospital Cardiac Arrest in Relation to Age and Early Identification of Patients With Minimal Chance of Long-Term SurvivalCLINICAL PERSPECTIVE. *Circulation*. 2015;131(18):1536-1545. doi:10.1161/CIRCULATIONAHA.114.013122.

147. Winther-Jensen M, Kjaergaard J, Wanscher M, et al. No difference in mortality between men and women after out-of-hospital cardiac arrest. *Resuscitation*. 2015;96:78-84. doi:10.1016/j.resuscitation.2015.06.030.

148. Rajan S, Folke F, Kragholm K, et al. Prolonged cardiopulmonary resuscitation and outcomes after out-of-hospital cardiac arrest. *Resuscitation*. 2016;105:45-51. doi:10.1016/j.resuscitation.2016.05.004.

149. Cortese G, Scheike TH, Martinussen T. Flexible survival regression modelling. *Stat Methods Med Res*. 2010;19(1):5-28. doi:10.1177/0962280209105022.

150. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393.

151. Bartlett JW, Seaman SR, White IR, Carpenter JR, Alzheimer's Disease Neuroimaging Initiative*. Multiple imputation of covariates by fully conditional specification: Accommodating the substantive model. *Stat Methods Med Res*. 2015;24(4):462-487. doi:10.1177/0962280214521348.

152. Shoemaker WC, Appel PL, Kram HB. Role of oxygen debt in the development of organ failure sepsis, and death in high-risk surgical patients. *Chest*. 1992;102(1):208-215. http://www.ncbi.nlm.nih.gov/pubmed/1623755. Accessed October 18, 2016.

153. Norman BC, Jackson JC, Graves JA, et al. Employment Outcomes After Critical Illness. *Crit Care Med*. 2016;44(11):2003-2009. doi:10.1097/CCM.0000000000001849.

154. Biering K, Hj?llund NH, Lund T. Methods in Measuring Return to Work: A Comparison of Measures of Return to Work Following Treatment of Coronary Heart Disease. *J Occup Rehabil*. 2013;23(3):400-405. doi:10.1007/s10926-012-9405-x.

155. Blichert-Hansen L, Nielsson MS, Nielsen RB, Christiansen CF, Nørgaard M. Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a

short report. *Clin Epidemiol*. 2013;5:9-12. doi:10.2147/CLEP.S37763.

156. Lauridsen MD, Gammelager H, Schmidt M, Nielsen H, Christiansen CF. Positive predictive value of International Classification of Diseases, 10th revision, diagnosis codes for cardiogenic, hypovolemic, and septic shock in the Danish National Patient Registry. *BMC Med Res Methodol*. 2015;15(1):23. doi:10.1186/s12874-015-0013-2.

157. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125.

158. Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: Accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Public Health*. 2007;35(5):497-502. doi:10.1080/14034940701271882.

159. Guidet B, De Lange DW, Christensen S, et al. Attitudes of physicians towards the care of critically ill elderly patients - a European survey. *Acta Anaesthesiol Scand*. 2018;62(2):207-219. doi:10.1111/aas.13021.

160. Flaatten H, de Lange DW, Artigas A, et al. The status of intensive care medicine research and a future agenda for very old patients in the ICU. *Intensive Care Med*. 2017;43(9):1319-1328. doi:10.1007/s00134-017-4718-z.

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