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PhD Thesis
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Cardiac arrest survival: Recovery and mental health

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Preface

The research presented in this thesis was conducted at the Department of Cardiology, Copenhagen University Hospital – Rigshospitalet and also carried out in the other four Heart Centres in Denmark, the Neurobiology Research Unit (NRU) at Copenhagen University Hospital – Rigshospitalet and at the Danish Knowledge Centre for Rehabilitation and Palliative Care (REHPA), University of Southern Denmark and Odense University Hospital.

With a clinical background in cardiology and intensive care, I have focused professionally on cardiac arrest survivors and their close relatives for several years. During the years I worked in intensive care, it became clear that cardiac arrest systems of care often stop short after transfer from the intensive care unit to the medical ward and that the health care system often provides a fragmented approach regarding post-cardiac arrest hospital discharge planning. While employed as a clinical nurse specialist at the Department of Cardiology at Rigshospitalet in autumn 2015, I was given the opportunity to examine the gaps in care for cardiac arrest survivors in Denmark. Alongside the establishment of a clinical outpatient clinic for cardiac arrest survivors, a highly relevant multidisciplinary clinical and research network was established with the Department of Occupational Therapy and Physiotherapy at Copenhagen University Hospital – Rigshospitalet. This joint network led to the development of a clinical safety net for cardiac arrest survivors in the Department of Cardiology at Rigshospitalet, particularly aimed at identifying cognitive impairment in the survival trajectory. This collaboration also led to the publication of two research papers.[1,2]

During the PhD programme, I visited Maastricht University Hospital and the Adelante Centre of Expertise in Rehabilitation and Audiology, Hoensbroek, The Netherlands. This research visit led to the publication of a collaborative research paper.[3]

I worked part-time on my PhD from October 2017 to February 2023.

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This thesis would not have been possible if not for the Danish Knowledge Centre for Rehabilitation and Palliative Care (REHPA) and the national Danish Cardiac Arrest Survivorship (DANCAS) network. In particular, I would like to thank *Ann Dorthe Zwisler* and *Vicky Joshi*. I am eternally grateful for our joint discussions on cardiac arrest survivorship and for the REHPA stay for cardiac arrest survivors in Denmark. *Ann Dorthe*, you are a huge inspiration, and I look forward to continuing our collaboration on cardiac arrest survivorship in the future.

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Mette Kirstine Wagner
Copenhagen, February 2023

List of papers

This PhD thesis is the result of research performed with numerous colleagues working in various institutions across Denmark. The data were collected between 2014 and 2022 and published in:

Paper 1 (DenHeart cross-sectional substudy), Paper 2a (Design paper for REVIVAL study), Paper 2b (REVIVAL outcome study) and Paper 3 (Qualitative focus group study).

Paper 1

Wagner MK, Christensen AV, Hassager C, Stenbæk DS, Ekholm O, Borregaard B, Thrysoee L, Rasmussen TB, Thorup CB, Mols RE, Juel K, Berg SK. Sex Differences in Patient-Reported Outcomes in the Immediate Recovery Period After Resuscitation: Findings From the Cross-sectional DenHeart Survey. *J Cardiovasc Nurs*. April 2022.
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Paper 2a

Wagner MK, Berg SK, Hassager C, Armand S, Møller JE, Ekholm O, Rasmussen TB, Fisher P, Knudsen GM, Stenbæk DS. Cognitive impairment and psychopathology in out-of-hospital cardiac arrest survivors in Denmark: The REVIVAL cohort study protocol. *BMJ Open*. August 2020. doi: 10.1136/bmjopen-2020-038633

Paper 2b

Wagner MK, Berg SK, Hassager C, Borregaard B, Rasmussen TB, Ekholm O, Stenbæk DS. Cognitive impairment and psychopathology in sudden out-of-hospital cardiac arrest survivors: Results from the REVIVAL cohort study. Manuscript in final preparation.

Paper 3

Wagner MK, Berg SK, Tang LH, Stenbæk DS, Hassager C, Missel M. Understanding the lived experiences of short- and long-term consequences on daily life after out-of-hospital cardiac arrest: A focus group study. *J Adv Nurs*. *J Adv Nurs.* 2021 Mar;77(3):1442-1452.
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Abbreviations

B-IPQ	Brief Illness Perception Questionnaire
CI	Confidence interval
COSCA	Core Outcome Set for Cardiac Arrest
CPC	Glasgow-Pittsburgh Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
DANCAS	Danish Cardiac Arrest Survivorship
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ERC	European Resuscitation Council
ESAS	Edmonton Symptom Assessment Scale
ESICM	European Society of Intensive Care Medicine
HADS	Hospital Anxiety and Depression Scale
HeartQoL	Heart-related Quality of Life Questionnaire
HRQoL	Health-related quality of life
ICF	International Classification of Function, Disability and Health
ICU	Intensive care unit
IES	Impact of Event Scale
IES-R	Impact of Event Scale – revised
MoCA	Montreal Cognitive Assessment
mRS	Modified Rankin Scale
nFO	Non-favourable outcome
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
REHPA	Danish Knowledge Centre for Rehabilitation and Palliative Care
ROSC	Return of spontaneous circulation
PICS	Post-intensive care syndrome
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
PTSD	Post-traumatic stress disorder
QoL	Quality of life
SD	Standard deviation
SF-12	Short Form-12 Health Survey
TT	Transitions theory
WHO	World Health Organization

Summary

Out-of-hospital cardiac arrest (OHCA) continues to be associated with high mortality rates worldwide. In Denmark, which has a population of almost 5.9 million, more than 5,000 suffer from it annually but the optimisation of critical steps in the chain of survival means that more people survive than ever before. Due to the risk of hypoxia to the brain and the trauma-related consequences of survival, mental health challenges pose an array of issues for some cardiac arrest survivors that affects their participation in society, including return to work and quality of life. Although post-resuscitation guidelines recognise the importance of addressing health outcomes that capture what really matters to cardiac arrest survivors, little is known about the early recovery and mental health burden from a patient-centred point of view. In particular, current evidence is insufficient in terms of early needs assessment of mental health and the experience of returning to daily life after survival. To address this gap in evidence, cross-sectional, prospective cohort and qualitative interview study designs were employed in the three studies in this PhD project. More specifically the objectives of this PhD were to: 1) examine patient-reported outcomes in the immediate recovery period after resuscitation, 2) investigate the efficacy of an early screening procedure to predict the risk of mental health challenges after resuscitation and 3) explore the consequences patient experiences in daily life after resuscitation.

Study 1 examined sex-differences in patient-reported outcomes in 176 OHCA survivors using five patient-reported outcome measures for symptoms of anxiety and depression (Hospital Anxiety and Depression Scale (HADS)), illness perception (Brief Illness Perception Questionnaire), symptom burden (Edmonton Symptom Assessment Scale), health status (Short Form-12) and health-related quality of life (HeartQoL) from the nationwide cross-sectional DenHeart study. Study 2 (REVIVAL) investigated a novel screening procedure at three Danish heart centres that comprised screening for cognitive impairment using the Montreal Cognitive Assessment (MoCA), and symptoms of psychopathology using HADS and the Impact of Event Scale–Revised (IES–R) in 297 OHCA survivors during hospitalisation, while the evolution of these parameters at the three-month follow-up used a neuropsychological test battery and repeated HADS and IES–R. Finally, Study 3 explored the experiences of surviving cardiac arrest and its impact on daily life via six focus groups interviews with OHCA survivors (n=32) attending a national rehabilitation programme.

Study 1 found that female survivors were more likely to report negative health consequences and worse patient-reported outcomes at hospital discharge from a heart centre when compared to their male counterparts. Particularly symptoms of anxiety and fatigue were most prevalent in female cardiac arrest survivors. Study 2 demonstrated that cognitive impairment and symptoms of psychopathology were common during hospitalisation. Moreover, we found associations between early cognitive impairment and a non-favourable cognitive outcome at three-month follow-up, between early symptoms of anxiety and clinical levels of anxiety at three months, early symptoms of depression and clinical levels of depression at three months, and between early symptoms of traumatic distress and clinical levels of post-traumatic stress disorder at follow-up. Study 3 indicated that the survivors experienced distinct bodily impairments, mental suffering and a loss of sense of self from early on to several years after resuscitation. Moreover, the participants described the need for emotional support and receiving a helping hand early in addressing care needs from the health care system.

In conclusion, Danish OHCA survivors experience considerable secondary mental health challenges in their immediate and early recovery as well as consequences in terms of their return to daily life after resuscitation. Overall, the findings indicate that early, routine screening of cognitive impairment and symptoms of psychopathology during hospitalisation (MoCA, HADS and IES-R) can potentially be used to provide risk markers of prolonged mental health challenges at a critical point before hospital discharge for survivors of OHCA undergoing transitions.

Dansk resumé

Hjertestop uden for hospitalet er på verdensplan fortsat forbundet med høj dødelighed. I Danmark, som har en befolkning på næsten 5,9 millioner, får mere end 5.000 årligt hjertestop udenfor hospitalet. Som et resultat af en optimering af kritiske trin i overlevelseskæden, overlever flere mennesker heldigvis end nogensinde før, i dag hjertestop udenfor hospitalet. På grund af risikoen for iltmangel til hjernen og traume-relaterede konsekvenser af hjertestop og overlevelse, oplever adskillige hjertestopoverlevere mentale helbredsudfordringer. Disse mentale helbredsudfordringer påvirker deltagelse i samfundet, herunder tilbagevenden til arbejdet og livskvaliteten. Selvom internationale genoplivningsguidelines har anerkendt vigtigheden af at tage fat på de helbredsudfordringer, der har stor betydning for overlevere af hjertestop, er der fortsat begrænset viden omkring den tidlige restitutionsperiode og de mentale helbredsudfordringer set fra et patientcentreret perspektiv. Især er nuværende viden sparsom, når det kommer til en tidlig behovsvurdering af den mentale helbredstilstand og oplevelsen af at vende tilbage til hverdagslivet efter overlevet hjertestop. For at imødegå den manglende viden, blev der med dette PhD projekt igangsat tre studier med hhv. et tværsnits-, et prospektivt kohorte- og et kvalitativt interviewstudie design. Mere specifikt var formålene med projektet at: 1) undersøge patient rapporterede oplysninger i den umiddelbare restitutionsperiode efter genoplivning, 2) undersøge effektiviteten af en tidlig screeningsprocedure til at forudsige risikoen for mentale helbredsudfordringer efter genoplivning og 3) undersøge de konsekvenser overlevere efter hjertestop oplever i hverdagen efter genoplivning.

Studie 1 undersøgte kønsforskelle i patient-rapporterede oplysninger hos 176 hjertestopoverlevere ved brug af fem selvrapportede spørgeskemaer der måler symptomer på angst og depression (Hospital Anxiety and Depression Scale (HADS)), sygdomsopfattelse (Brief Illness Perception Questionnaire), symptombyrde (Edmonton Symptom Assessment Scale), helbredsopfattelse (Short Form-12) og helbredsrelateret livskvalitet (HeartQoL) fra det nationale tværsnitsstudie, DenHeart. Studie 2 (REVIVAL) undersøgte en screeningsprocedure på tre Hjertecentre i Danmark. Screeningsproceduren bestod af en kognitiv screening med Montreal Cognitive Assessment (MoCA) og psykopatologiske symptomer med HADS og Impact of Event Scale – revised (IES-R) hos 297 hjertestopoverlevere under indlæggelsen, mens et neuropsykologisk testbatteri og gentagelse af HADS og IES-R blev anvendt ved tre måneders opfølgning.

Afslutningsvis udforskede studie 3 de levede erfaringer af at overleve hjertestop og konsekvenserne af tilbagevenden til hverdagslivet ved hjælp af seks fokusgruppeinterviews af overlevere efter hjertestop (n=32) som deltog i et rehabiliteringsprogram.

Studie 1 fandt, at kvindelige overlevere var mere tilbøjelige til at rapportere negative helbredskonsekvenser og dårligere patient-rapporterede oplysninger ved udskrivelsen fra et hjertecenter sammenlignet med mændene. Især var symptomer på angst og fatigue mere prævalent hos kvinderne. Studie 2 demonstrerede, at kognitive følger og symptomer på psykopatologi er almindeligt under indlæggelsen. Vi fandt sammenhænge mellem tidlige kognitive følger og et ikke favorabelt kognitivt outcome ved tre måneders opfølgning. Desuden fandt vi sammenhænge mellem tidlige symptomer på angst og kliniske niveauer af angst ved tre måneders opfølgning, mellem tidlige symptomer på depression og kliniske niveauer af depression ved tre måneders opfølgning og mellem tidlige symptomer på traumatisk stress og kliniske niveauer af post-traumatisk stress syndrom (PTSD) ved tre måneders opfølgning. Studie 3 indikerede, at patienter genoplivet efter hjertestop oplevede udtalte kropslige følger, mental lidelse og tab af selvopfattelsen fra tidligt i forløbet op til flere år efter hjertestop. Ydermere beskrev deltagerne et behov for tidlig følelsesmæssig støtte og hjælp til at få adresseret omsorgsbehov fra sundhedssystemet.

På baggrund af fundene i PhD projektet kan det konkluderes, at danske patienter genoplivet efter hjertestop udenfor hospitalet oplever udtalte sekundære helbredsrelaterede mentale udfordringer i den umiddelbare og tidlige restitutionsperiode med konsekvenser for deres tilbagevenden til hverdagen. Samlet set indikerer resultaterne, at udskrivelsen fra hospitalet til hjemmet er et kritisk transitionstidspunkt for overlevere efter hjertestop og at en rutinemæssig screeningsmetode for kognitive følger og symptomer på psykopatologi under indlæggelsen (MoCA, HADS and IES-R) har potentiale som risikomarkører for længerevarende mentale helbredsudfordringer.

Introduction

As more people survive sudden out-of-hospital cardiac arrest (OHCA), recovery and survivorship after resuscitation has received increased attention in recent years. Historically survival has been the core outcome. Due to extensive research on pre- and in-hospital OHCA management major improvements in survival rates have been reported, with today's rates higher than ever before.

A paradigm shift from mere survival to recovery and life after cardiac arrest has occurred since 2015. Most recently the Core Outcome Set for Cardiac Arrest (COSCA) initiative proposed to shift focus to comprehensively addressing an array of important health outcomes that encompass what really matters to cardiac arrest survivors. In sharp contrast to the importance of survival there is a substantial post-cardiac arrest mental health burden that is highly overlooked by health care professionals. In terms of neuropsychological function and well-being traditional short-term outcome measures are predominantly weighted by clinicians, with little or no attention given to patient-reported views or experiences following resuscitation. In an effort to understand mental health after OHCA minor studies have begun questioning whether the most vulnerable survivors will recover without patient-derived assessments.

From a patient-centred point of view, even though the number of cardiac arrest survivors discharged from hospital is rising limited attention has been paid to gaps in mental health knowledge on immediate recovery, early markers of long-term outcomes and impact on daily life. Consequently, specific post-cardiac arrest guidance on mental health challenges remains suboptimal. To address these knowledge gaps this thesis aimed to closely:

- examine patient-reported outcomes (PROs) in the immediate recovery period after resuscitation
- investigate the efficacy of an early screening procedure to predict the risk of mental health challenges after resuscitation
- explore the consequences patients experience in daily life after resuscitation

As a result, three distinct methodologies were applied: a cross-sectional study design, a cohort study design and a qualitative interview design based on transitions theory (TT).

Background

Definition and epidemiology of OHCA

OHCA is an unexpected life-threatening condition that occurs in a community setting. The sudden onset of cardiac arrest is defined as "the loss of mechanical cardiac function and the absence of systemic circulation" [4] and leads to whole-body ischemia that affects organ function. In particular areas of the brain, such as the hippocampus, thalamus, amygdala, visual cortex and frontal lobes are especially vulnerable to hypoxia.[5]

In Europe[6] and the United States[7], OHCA affects more than 300,000 people annually. Cardiovascular disease, particularly coronary artery disease, is the primary cause of OHCA.[8] This time-critical medical emergency is still associated with high mortality rates worldwide.[8] However, as a result of extensive resuscitation research, more people currently survive OHCA than ever before.[9] As a result, the number of cardiac arrest survivors admitted to hospital globally has increased. In Europe the survival rates at hospital discharge range from 0–18%, or 8% on average.[7] In Denmark the 30-day survival rate has increased considerably to 14% over the last 20 years[9] due to a fourfold increase in the initiation of resuscitation before an ambulance arrives and an increase in the number of defibrillators available in public spaces. Three out of four OHCAs in Denmark occur in private residences and approximately 80% of Danish OHCA survivors are male.[10]

Survival after cardiac arrest depends on various factors besides resuscitation. The evidence suggests that heterogeneity exists for sex[11,12], comorbidities[13], location[14], socioeconomic status[15] and various lifestyle factors.[8] Likewise, a conscious state at admission is positively associated with 30-day survival after OHCA[15]. Notably hypoxic-ischemic brain injury after resuscitation is a common cause of death[16] and accounts for about 65% of in-hospital mortality in the intensive care unit (ICU) with coma following OHCA.[17] Nevertheless most OHCA survivors are discharged from hospital with a good neurological outcome, indicating that they will be able to return to normal activities and be able to manage daily life independently.

Cardiac arrest systems of care

The chain of survival

The core outcome when treating cardiac arrest is to provide the patients with prompt, high-quality care that saves their lives. Survival after cardiac arrest and cardiopulmonary resuscitation depends on a time-sensitive sequence of interventions called the chain of survival (Figure 1).[16] The out-of-hospital chain of survival for adults comprises four links: early recognition and activation of emergency medical services, early bystander CPR to oxygenate and circulate blood to all organs, early defibrillation to eliminate abnormal heart rhythm and early advanced life support and standardised post-resuscitation care.[16] A strong chain improves the chances of survival, a good outcome and recovery from OHCA.[17]

Figure 1. Out-of-hospital chain of survival for adults. Adapted from the European Resuscitation Council Guidelines 2021: Systems saving lives.

The fourth link: Post-resuscitation care

The initial post-resuscitation care starts immediately after the return of spontaneous circulation (ROSC).[18] Regardless of whether the patient is awake or in a coma the primary in-hospital target is to reduce mortality (save the heart and the brain) and enhance quality of life (QoL).[6,18] As previously mentioned a shift from mere survival to recovery and survivorship, i.e. the state of being a survivor of cardiac arrest, has occurred. Hence, the secondary mental health consequences of resuscitation are more widely recognised.[19,20] In 2010 Iwashyna argued that the impact of surviving critical illness on people's lives was often overlooked in critical care and that there was an urgent need to develop new approaches in which survivors were powerful partners in addressing the challenges that went beyond survival.[21] In 2018 COSCA was published.[20] The initiative emphasised the need to shift attention to comprehensively addressing a wide array of important health outcomes that capture what really matters to cardiac arrest survivors. The most recent

European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) Guidelines: Post-Resuscitation Care[20] recognises the importance of survivorship after cardiac arrest from a patient-centred point of view more heavily. To facilitate higher quality of care after OHCA more research is still needed on immediate patient-reported mental health outcomes, early assessment of mental health status, predictive factors of patient mental health status and survival experiences, not to mention the subsequent impact on daily life. As a result the following sections will look closely at the existing literature.

Mental health

According to a recent World Health Organization (WHO) position paper, mental health and brain health are two closely related concepts .[22] Although brain health refers to the structure and function of brain cells and neurotransmitters, and mental health to a manifestation of symptoms due to changes in the brain, this dissertation will apply a holistic approach to delineate its focus on mental health. In this thesis, mental health refers to neuropsychological impairment in terms of neurocognitive, emotional and psychological well-being (or their absence) following OHCA.

Mental health challenges cardiac arrest survivors face

Due to hypoxia to the brain during cardiac arrest, concomitant post-resuscitation care, a life-or-death experience, a cardiac diagnosis, or as secondary prevention of another sudden cardiac arrest with the insertion of an implantable cardioverter defibrillator, mental health is an area of significant concern for several OHCA survivors.[6,23–26] The body of evidence on the mental health challenges cardiac arrest survivors face will be described below.

Neurocognitive impairment

Although the majority of OHCA survivors recover well, the scale of disability resulting from hypoxic-ischemic brain injury ranges from complete recovery to coma or even death.[24] The most prevalent and challenging neurological residual sequela in survivors of OHCA is neurocognitive impairment.[25] According to Ashcraft and Radvansky, cognition is “the complex array of mental processes involved in remembering, perceiving, thinking, and how these processes are employed” and serves as an umbrella term for higher-order thinking.[27] There is no universal consensus on the number and distribution of cognitive domains. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) however, contains a framework for neurocognitive disorders, including for acquired deficits that represent "decline from a previously attained level of cognitive functioning, and are not neurodevelopmental deficits present from birth or early life".[28] Overall DSM-5 highlights six neurocognitive domains: complex attention, executive functioning, learning and memory, language, perceptual–motor functioning and social cognition (Figure 2).

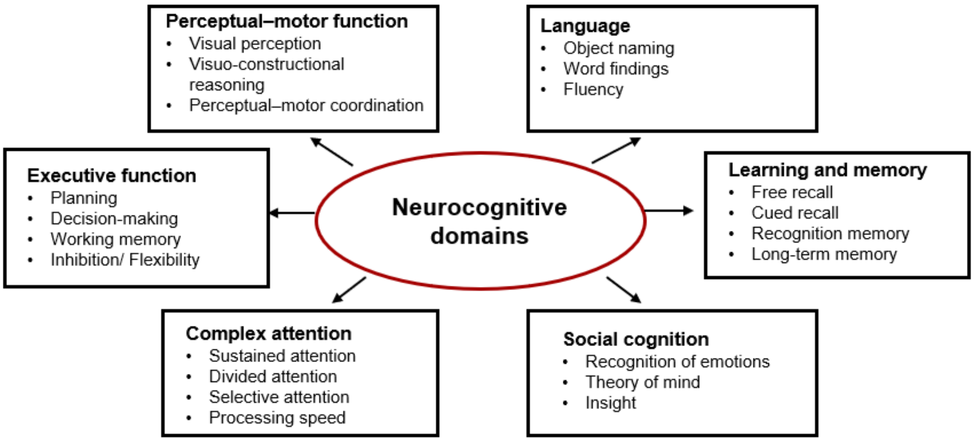


Figure 2. Neurocognitive domains with subdomains. Adapted from Classifying neurocognitive disorders: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

When classifying neurocognitive impairment in survivors of cardiac arrest the majority have subtle to moderate impairment.[29] Reviews summarising prevalence show a broad range of occurrence from no impairment at all to 100% cases in survivors.[29-31] The prevalence of cognitive impairment is nevertheless expected to be high. A recent systematic review (2022) examining neurocognitive function following cardiac arrest demonstrated incidence of cognitive impairment of 54–88% in survivors using the Montreal Cognitive Assessment (MoCA), a standard cognitive screening tool.[31,32] As noted in previous reviews memory problems and executive functioning are the two cognitive domains predominantly affected[29-31,33], though all cognitive domains appear to be affected to a certain extent. Roughly half of OHCA survivors experience long-term cognitive impairment that persists well beyond the acute hospitalisation.[34-36] However, wide follow-up times are reported.[31] To our knowledge only few previous resuscitation studies have explored and screened for cognitive impairment in the early phase during hospitalisation using MoCA. The prevalence of cognitive impairment in these studies[37,38] is difficult to establish as the study samples were small (n=50 (38 initially and then 12) and n=3). Moreover reviews and an American Heart Association report state that there is limited data on the relationship between early signs of cognitive impairment and long-term cognitive challenges after resuscitation.[26,29,31,39]

Neurocognitive impairment after cardiac arrest survival may occur for reasons other than hypoxia to the brain during resuscitation, e.g. pre-existing cardiovascular disease and the critical illness trajectory.[24,34] The vast majority of OHCA survivors are admitted to the ICU and critically ill patients are generally susceptible to developing neuropsychiatric sequelae.[40] The frequent and late complications that critical illness causes are known as post-intensive care syndrome (PICS).[41] A central aspect of PICS is any remaining cognitive impairment but also associated anxiety, depression, post-traumatic stress disorder (PTSD)[42] and fatigue[24]. PICS is associated with poor QoL after discharge from hospital.[43] Overall cognitive impairment may markedly alter the level of social participation[44,45], return to work[45] and QoL[46--50] after cardiac arrest. Importantly, as hypoxic-ischemic brain injury increases the risk of developing anxiety, depression and PTSD[51], close caregivers are also adversely affected when the survivor exhibits cognitive challenges.[52]

Symptoms of psychopathology

Experiencing and surviving sudden cardiac death may impose a profound emotional and psychological burden on the survivor. The presence of symptoms of psychopathology, i.e. the study and processes of mental disorders, after resuscitation have been acknowledged and studied more extensively in the past few years. Combined, they comprise trauma responses[3,45,53,54], behavioural problems, emotional lability[36] and symptoms of anxiety, depression and PTSD.[26,43,53,55-59] In the following the diagnostic criteria for Generalised Anxiety Disorder, depression, trauma reactions and PTSD based on DSM-5[60] are described.

To be diagnosed with Generalised Anxiety Disorder patients must have experienced core symptoms such as excessive anxiety and worry (apprehensive expectations), occurring more days than not for at least six months concerning various events or activities, e.g. work or school performance, and must find it difficult to control their worry. The symptoms must be associated with three or more of the symptoms listed in Table 1.

Table 1. Diagnostic criteria for Generalised Anxiety Disorder. Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Symptom	**Description**
1	Restlessness, feeling keyed up or on edge
2	Easily fatigued
3	Difficulty concentrating or mind going blank
4	Irritability
5	Muscle tension
6	Sleep disturbance

To meet the diagnostic criteria for depression at least five or more symptoms should be present in the same two-week period, at least one of which should be either depressed mood or loss of interest or pleasure (Table 2).

Table 2. Diagnostic criteria for depression. Adapted from the Diagnostic and Statistical Manual of Mental Disorders fifth edition.

Symptom	**Description**
1	Depressed mood most of the day nearly every day
2	Loss of interest and enjoyment in activities most of the day nearly every day
3	Significant weight loss when not dieting, or weight gain or decrease or increase in appetite nearly every day
4	Slowing down of thought and reduction in physical movement (observable by others, not merely subjective feelings of restlessness or slowing down)
5	Fatigue or loss of energy nearly every day
6	Feelings of worthlessness or excessive or inappropriate guilt nearly every day
7	Diminished ability to think or concentrate, or indecisiveness, nearly every day
8	Recurrent thoughts of death

In particular acute traumatic stress, a key factor in developing PTSD, is characterised by “behavioral and cognitive processes of re-experiencing and avoiding reminders of the event [cardiac arrest]”.[61] Traumatic reactions are described as acute stress disorder when present in the first month after the traumatic event, and as PTSD if the symptoms last longer than one month.[60] Table 3 lists the criteria for PTSD.

Table 3. Diagnostic criteria for post-traumatic stress. Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Criterion	Description
A	Traumatic stressor (cardiac arrest)
B	Intrusive re-experiencing of the event (e.g. traumatic nightmares or flashbacks)
C	Avoidance of reminders of the traumatic event
D	Alterations in arousal and reactivity (e.g. hypervigilance, exaggerated startle response or irritability)
E	Negative alterations in mood and cognition (e.g. persistent negative affect or self-perception, or amnesia not caused by alcohol, head injury and/or drugs regarding key aspects of the trauma)

Similar to neurocognitive impairment, estimates of the frequency of symptoms of psychopathology after OHCA have been published with widely disparate incidence rates. Thus evidence suggests that a substantial number of survivors suffer long-term psychopathology. In a recent systematic review and meta-analysis (2021) Yaow et al. demonstrate that OHCA survivors report a higher rate of anxiety, depression and PTSD compared to the general population.[62] Using the PRO instrument Hospital Anxiety and Depression Scale (HADS), which is most commonly used to quantify symptoms of anxiety and depression in resuscitation research[62], an overall prevalence of post-resuscitation anxiety in reported up to 30% of survivors for 12 months after survival.[44,55,57] Depression symptoms were reported six months after hospital discharge with nearly the same frequency. Hence, depression symptoms decrease when reported 12 months after survival.[44,53,55,57] Trauma reactions and PTSD are less well-examined in this population, and researchers use a variety of measures and cut-off values.[26,62] PTSD, however, is found to occur in approximately one in every three individuals after cardiac arrest and persists in around one in four survivors.[53,58]

Looking at change over time early emotional distress after surviving OHCA have not received much attention. Few longitudinal cohort studies have identified these immediate in-hospital reactions; hence, knowledge on their association to long-term psychopathology is sparce. In 2002 Kamphuis et al. found cardiac arrest survivors with exceedingly high rates of anxiety and depression during hospitalisation.[63] However, on the whole, these distressing symptoms were identical after 12 months using less common screening tools with no definitive cut-offs for determining anxiety and depression. Larsson et al.[64] reported that fewer symptoms of anxiety and depression (HADS) at discharge were associated with better health-related QoL (HRQoL). Symptoms of psychopathology after returning home remained unreported. Still, the prevalence of psychopathology after OHCA is profound and is negatively associated with health behaviours such as low physical activity, poor sleep quality[65] and the risk of cardiovascular disease. In addition psychological distress is negatively associated to societal reintegration[65], while a history of trauma exposures is linked to the development of PTSD. In general depression[55] and also apathy (a clinical symptom of depressive behaviour)[66] are associated with not only a poor neurological outcome but also worse QoL.[33]

Mental health assessment after cardiac arrest

International recommendations on mental health assessment after OHCA encompass the detection of neurocognitive impairment and emotional problems before discharge.[18,26] According to the evidence, mental health issues in cardiac arrest survivors are frequently overlooked and not systematically assessed.[29,31] A core outcome set has nevertheless not been established, just as the timing of mental health measurements is not stipulated. In the absence of evidence, early needs assessment identifying post-cardiac arrest mental health challenges before hospital discharge is currently offered based on limited scientific documentation.

Assessment of neurocognitive impairment

Traditionally post-resuscitation neurological outcomes rely on functional disability scales such as the five-point Glasgow-Pittsburgh Cerebral Performance Category (CPC) Scale (1–5), and/or the seven-point (0–6) modified Rankin Scale (mRS).[67] In recent years however the trustworthiness of these clinician-rated functional scales has been debated due to their inability to discriminate between levels of cognitive function in a refined way. The ERC ESICM has recommended MoCA[23] since the publication of Moulaert et al.’s systematic review on screening for cognitive impairment.[29] Underpinning this recommendation is a recent study by van Gils et al., who also found that MoCA is a valid cognitive screening instrument for use in the OHCA patient population.[68] However, data from this cohort was not solely collected upon discharge. Overall research emphasises the importance of an early and sensitive bedside screening followed by a detailed neurocognitive assessment done later in selected survivors.[39,69] At present the paucity of research in this field is suboptimal. Therefore, it seems imperative to include cognitive assessment to facilitate the recovery process since cognitive recovery may be limited to three months after cardiac arrest[24,44,47] and since survivors highlight cognitive recovery as a key factor in the individual recovery process.[67]

Assessment of symptoms of psychopathology

Over time it has become indisputable that subjective information reported by patients is central in health care research, which is also in line with current resuscitation research.[70-72] Recently, PROs have been increasingly used to measure emotional problems and manifestations of psychopathology in research and clinical practice after resuscitation. PRO measures (PROMs) are powerful tools used to obtain data on patients' subjective symptom burden, functional status, mental health and HRQoL.[73] However, a PROM for cardiac arrest survivors has yet to be developed, preventing health care professionals from comprehensively capturing the range of outcomes that matter to survivors. As previously stated the literature is inconclusive in terms of measures used to assess anxiety, depression and PTSD[59,70], which is why identifying these symptoms seems crucial to prevent long-term psychopathological manifestations. In recent post-resuscitation care guidelines, HADS has been proposed as an early but also repetitive measure of symptoms of anxiety and depression. Previously the Impact of the Event Scale (IES) has been suggested as a screening tool for symptoms of PTSD.[23] However, the predictive value of developing psychopathology using these tools is unknown.

Post-cardiac arrest screening for fatigue is recommended.[18] Decreased social participation and diminished return to work is found to be associated with fatigue.[74] Again, a lack of short-term patient-reported assessment guidance on the burden of fatigue symptoms exists.[26] To understand and capture the patient-reported affective burden after resuscitation, Sawyer et al. emphasised that research might need to include more somatic symptoms to understand post-cardiac arrest health outcomes and to identify the most vulnerable survivors in need of appropriate care.[26]

Sex differences in PROs

Women are more likely than men to be diagnosed with anxiety, depression and PTSD in relation to symptoms of psychopathology and mental illness. Even though men have a three-fold risk of cardiac arrest across all age groups, this is also the case regarding worse patient-reported mental health outcomes after resuscitation.[57,56,75,76] The immediate mental health response, symptom burden and illness perception of the trauma of surviving cardiac arrest nevertheless remains unknown. In a Dutch population Armand et al. found that female survivors had higher acute traumatic stress scores compared to males in a mixed cohort of in- and OHCA survivors.[3] In a recent review on psychological distress after sudden cardiac arrest and its impact on recovery Agarwal et al. demonstrated the urgent need for assessing psychological sequelae after cardiac arrest.[65] In particular psychological distress was associated with an increased risk of negatively affecting the recovery process. As female survivors are more susceptible to emotional reactions and psychopathology, collecting PROMs from both sexes is a necessity in terms of helping future survivors and clinicians identify at-risk survivors to take initiatives to improve the mental health status and support the recovery process.

The lived experience after resuscitation

The recovery process can take months or even years after cardiac arrest survival. For many survivors the sudden onset of OHCA is an upheaval that can shake the foundations of their daily life. The experience of cardiac arrest is individual, however, and the recovery process and transition to cardiac arrest survivorship occurs on an individual timeline.[26] Previous studies exploring the lived experience of surviving cardiac arrest have found that survivors of OHCA face mental health challenges.[77,78] Interview studies describe how cardiac arrest survivors have an increased awareness of what is particularly important to them in life. Previous studies, however, sparsely describe the impact on daily life, how survivors adapt to changes and what their perspective on managing their return to life is. In addition, most studies have described the experiences of cardiac arrest survivors using a non-theoretical approach to interpret findings.[77,79-82] To improve the post-cardiac arrest transition to daily life international guidelines call for focusing on unmet recovery needs to improve care.[6,26]

Framework for outcome research in survivors of cardiac arrest

Research on outcomes in post-resuscitation care has previously used the International Classification of Function, Disability and Health (ICF) of the World Health Organisation (WHO) as a framework.[44,83,84] Survivors of OHCA are a heterogeneous population, which means this disruptive event affects healthy individuals of all ages, i.e. it is not just age-related, and both sexes in their most productive years, causing a prolonged and substantially negative impact on their mental health. Post-resuscitation recovery is often complex due to the multiple factors that may affect the process. Consequently the ICF's bio-psychosocial model of illness and individual health consequences provides a holistic view of the numerous secondary consequences of survival. From a survivor perspective however mental health and associated assessments in the initial stages of recovery after OHCA are not well understood, implying that the complexity of the ICF framework is unsuitable for use and implementation in a hospital setting. This indicates that it is time to change focus. Current post-resuscitation care guidelines have started to recognise the impact of therapy on the mental health of survivors, placing more emphasis on PROs and individual experiences of the recovery process as opposed to solely treatment outcomes[6,26,85], neurological impairments and physical disability. In 2020 the American Heart Association made recovery from sudden cardiac arrest a novel link in its updated chain of survival.[85] New recommendations were enhanced to include discharge planning. Still, the evidence supporting these recommendations falls short due to limited data and low-quality studies.

The recovery process and TT

Recovery is ambiguously defined, which also makes comparing results difficult. The Cambridge Dictionary's generic definition of the verb recovery is "to get better after an illness"[86], but other fields demarcate it more expansively. The psychosocial literature, for example, challenges previous medical definitions of recovery, advocating that focusing solely on the remission of symptoms and return to prior functioning is too narrow and must incorporate the development of new meaning and purpose in life. The most recent Danish white book on rehabilitation describes recovery and rehabilitation as two intertwined processes, where the latter is based on the professional's point of view and the former from the patient's point of view.[87] According to Meleis' widely applicable and comprehensive middle-range transitions theory (TT) the recovery process is a key part of health and illness transitions[88], and important to understand to improve quality of care (Figure 3).

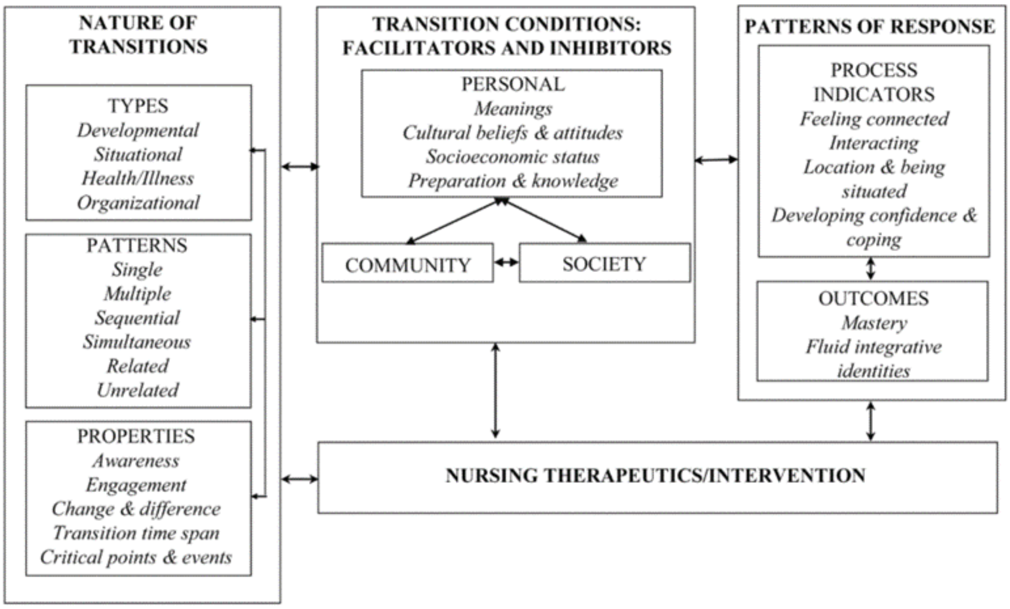


Figure 3. Middle-Range Transitions Theory. Adapted from Meleis, A.I., Sawyer, L.M., Im, E.O., Hilfinger Messias D.K. and Schumacher, K. (2000). Experiencing transitions: An emerging middle-range theory. Advances in Nursing Science, 23(1), 12–28.)

Meleis and colleagues propose various types and patterns of transitions along the health and illness continuum. These transitions are triggered by an event that changes the way individuals look at themselves and/or implies the end of how life was prior to the event.[89] Overall Meleis et al. describe transition as “a passage from one life phase, condition, or status to another and is embedded in the context of the particular situation”.[90] The TT adds the segments of individuals who do not make healthy transitions after illness and their patterns of response, contends that, to ease the recovery process, it is important to be aware of the critical points, for which appropriately congruent care is required. As pointed out, the immediate and early recovery during hospitalisation and hospital discharge might be critical points for survivors of OHCA undergoing transitions, recognising the significance of identifying the most vulnerable survivors in need of support and follow-up to facilitate healthy outcomes.

Summary and rationale for this thesis

In recent years the number of OHCA survivors has increased, which means that more and more survivors live with mental health consequences after resuscitation. A core outcome set does not exist, just as the timing of mental health measurements is not stipulated, which means these challenges can easily be neglected during hospitalisation, risking that mental health challenges will be overlooked. International guidelines suggest addressing an array of important health outcomes that encompass what really matters to cardiac arrest survivors. In terms of mental health the immediate recovery, early markers of long-term outcomes and the consequences of daily life have received minimal attention from a patient perspective. Minor studies have begun to question whether these survivors will recover without assessments that are more patient centred. Providing cardiac arrest survivors with continuity of care remains a challenge and a major issue that the health care system and health care providers currently face.

Aims

The overall research aim of this PhD thesis was to create new knowledge to address gaps in post-resuscitation care by exploring mental health outcomes in the early stages after the event and the consequences on daily life of surviving OHCA. Table 4 presents the overall objectives, secondary objectives, hypothesis and research questions.

Table 4. Thesis objectives, hypothesis and research questions

	Study 1	**Study 2**	**Study 3**
Overall objectives	Examines PROs in the immediate recovery period after resuscitation	Investigates the efficacy of an early screening procedure to predict the risk of mental health challenges after resuscitation	Explores the consequences patients experience in daily life after resuscitation
Secondary objectives	Examines sex differences in illness perception, symptom burden, anxiety, depression, HRQoL, and perceived health status in the immediate recovery period after resuscitation.	Investigates cognitive impairment, anxiety and depression symptoms and traumatic distress during hospitalisation Investigates the association between cognitive impairment during hospitalisation and cognitive outcome at the three-month follow-up, the association between symptoms of anxiety and clinical levels of anxiety at three-month follow-up, the association between symptoms of depression during hospitalisation and clinical levels of depression at three-month follow-up and symptoms of traumatic stress during hospitalisation and clinical levels of PTSD at three-month follow-up.	Explores and gains in-depth understanding of how OHCA survivors experience the short- and long-term consequences on daily life after resuscitation
Hypothesis		Cognitive impairment during hospitalisation is associated with a non-favourable cognitive outcome at the three-month follow-up, and symptoms of psychopathology during hospitalisation are associated with clinical levels of psychopathology at the three-month follow-up in a large cohort of OHCA survivors	
Research question	Describes sex differences in PROs at hospital discharge after resuscitation	Assesses the prevalence of cognitive impairment and symptoms of psychopathology during hospitalisation and whether these are associated with cognitive impairment and clinical levels of psychopathology at three-month follow-up after resuscitation	Addresses how cardiac arrest survivors experience daily life and what they emphasise as important in their return to daily life after resuscitation

PROs: Patient-reported outcomes, **HRQoL**: health-related quality of life; **PTSD**: post-traumatic stress disorder; **OHCA**: out-of-hospital cardiac arrest

As a result three distinct methodologies were applied: a cross-sectional study design (study 1), a cohort study design (study 2), and a qualitative interview design (study 3) based on TT, as outlined above.

Materials and methods

This chapter presents an overview of the methodologies, study populations, and data used in the thesis.

Study 1: Cross-sectional study (Paper 1)

Study design

Study 1, which solely used a cross-sectional design, was based on secondary data from the nationwide DenHeart Survey.[91] The original DenHeart survey combined PROMs at hospital discharge with one-year, register-based follow-up.

Study population, recruitment and setting

The original DenHeart survey was carried out across all diagnostic cardiac groups at five Danish heart centres from 15 April 2013 to 15 April 2014. A ward nurse invited all hospitalised cardiac patients to participate on a consecutive basis. They were asked to complete a packet of paper PRO questionnaires at discharge within three days and to return it by mail within four weeks. Patients who were <18 years of age, did not speak fluent Danish or did not have a civil registration number were excluded, as were patients hospitalised with a non-cardiac disease.

Clarification of study population and PROs

This study consecutively included adult patients resuscitated from OHCA identified based on the WHO International Classification of Diseases-10 diagnosis I46, including cardiac arrest without specification (I46.9), cardiac arrest with successful resuscitation (I46.0), and ventricular fibrillation (I49.0B). The following five PROMs were chosen because they measure subjective perceptions of various concepts, including somatic symptoms, just as they can provide an overall glimpse of how cardiac arrest and post-resuscitation care affect the mental health of survivors at an early stage: Hospital Anxiety and Depression Scale (HADS), Brief Illness Perception Questionnaire (B-IPQ), Edmonton Symptom Assessment Scale (ESAS), core Health-Related Quality of Life Questionnaire (HeartQoL), and Short Form-12 Health Survey (SF-12).

Ethical considerations

The institutional boards of the participating centres approved the DenHeart study, which complies with the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01926145). The Danish Data Protection Agency approved the handling of data (2007-58-0015/30-0937). All participants provided written informed consent.

Variables

Register data on sociodemographic variables were obtained from the Danish Civil Registration System (sex, age, marital and cohabitation status)[92], the Danish National Patient Register (level of comorbidity[1])[93], and the Danish Education Registers (highest level of completed education: no information available, elementary, upper secondary or vocational school, and higher education).[94] Comorbidity was calculated going back 10 years without the index discharge, and the Tu comorbidity index[95] was also calculated. Moreover clinical data were obtained from the Danish Clinical Quality Program – National Clinical Registry: The Danish Intensive Care Database.[96] Variables obtained were length of ICU admission (hours), mechanical ventilation yes/no, length of time on ventilator (hours), septic shock yes/no, and organ support therapy as use of inotropic agents yes/no. Register data and the clinical data were matched to the packet of Danish paper PRO questionnaires using hospital discharge date and discharge diagnosis compared to the date questionnaires were completed.

PROMs

Anxiety and depression

Recommended for use in cardiac populations, including for survivors of OHCA[18], HADS, which assesses self-reported mood disorders in medically ill non-psychiatric patients, comprises 14 items divided into two subscales measuring symptoms of anxiety and depression.[97] A threshold of ≥8 on each subscale was used to determine the presence of possible mood disorders. The validity, internal consistency, and reliability of the scale are good.[98,99]

Illness perception

B-IPQ[100], which assesses self-reported cognitive and emotional representations of illness, uses an eight-item scale measuring consequences, timeline, personal control, treatment control, identity, illness concern, emotional response and comprehensibility. The rank-order list (ninth item) was not included in the study. Items are rated on a ten-point Likert scale and whether a score is high or low represents different outcomes. Good validity and reliability have been found in cardiac populations.[101]

Symptom burden

ESAS[102] assesses self-reported intensity of nine symptoms: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. The severity of each symptom is rated on a 0-to-10 scale, 0 indicating an absence of symptoms and 10 their worst possible severity. Originally developed for cancer patients, ESAS is useful for measuring symptom burden in cardiac populations.[103]

Health-related quality of life

Based on items from three widely used questionnaires for specific groups of cardiac patients HeartQoL[104-106] measures self-reported HRQoL in coronary heart disease populations. There are 14 items divided into two subscales, physical (10 items) and emotional (4 items), rated rate on a 0-to-3 scale and resulting in an overall global score, with higher scores indicating better QoL. Good validity and reliability have been found in Danish recipients of an implantable cardioverter defibrillator.[106]

Health status

SF-12[107], which measures self-reported health status, comprises 12 items derived from SF-26. There are two components, physical component summary and mental component summary, which are subdivided into eight health domains: physical function, role – physical, bodily pain, general health, vitality, social functioning, role – emotional, and mental health. A higher score indicates better health status. SF-12 is suggested as a useful measure of HRQoL in patients resuscitated from OHCA.[108]

We also collected data from participants on the following ancillary variables: loneliness (one question), body mass index (weight and height), and health behaviour, e.g. smoking and alcohol habits.

Data analysis

Sociodemographic and clinical data related to the cardiac arrest were calculated using descriptive statistics. When comparing PROs, including the loneliness question, between female and male survivors, student *t*-tests, Pearson's chi-squared tests, and Fisher's exact tests were carried out as appropriate. Regression models were applied to calculate age-adjusted values. Data were analysed using Stata version 15.1 (Stata Corporation, College Station, Texas, USA) software on Statistics Denmark's research platform.

Study 2: Prospective cohort study (Papers 2a and 2b)

Study design

Study 2 is based on the Recovery after Cardiac Arrest Survival (REVIVAL) project, which is the multicentre prospective cohort study presented in Paper 2a.[109]

Study population, recruitment and setting

The REVIVAL study was carried out between December 2017 and February 2022 at cardiac arrest centres at Copenhagen University Hospital – Rigshospitalet, Odense University Hospital, and Herlev-Gentofte Hospital. Inclusion criteria were first-time adult survivors of OHCA due to a cardiac cause. Survivors with known brain diseases, serious untreatable somatic and psychiatric diseases, or who were not fluent in Danish language were excluded. A cardiac project nurse consecutively approached patients who were comatose when admitted at least 72 hours after sedatives were discontinued, while patients who were alert were approached when clinically stable.

Ethical considerations

Approved by the local regional Research Ethics Committee (H-18046155) and the Danish Data Protection Agency (RH-2017- 325, file no.05961) the REVIVAL study was conducted in accordance with the Declaration of Helsinki. After consulting with a close family member all survivors provided informed written consent.

Data collection and measures

After informed consent was obtained, sociodemographic variables (sex, age, cohabitation, ethnicity, level of education (according to the International Standard Classification of Education: Level 0-2: pre-primary, primary and lower secondary education, level 3 and 5: upper secondary education (high school) or vocational training and short-cycle tertiary education (there is no education corresponding to level 4 in Denmark), level 6-8: median length tertiary education, bachelor, master and PhD degrees[110], and occupational status), medical pre-arrest history (comorbidity), details on clinical characteristics related to cardiac arrest (place of OHCA, cause of OHCA, bystander-witnessed cardiac arrest, and CPR, initial shockable cardiac rhythm, time to ROSC (minutes), ICU treatment, mechanically ventilated, induced targeted temperature management, length of ICU stay (hours) and hospital admission (days) were collected from the medical charts.

Screening procedure

The hospital screening procedure consisted of a cognitive assessment administered using the Danish MoCA version 7.0®, info@mocatest.org and a PRO assessment of symptoms of psychopathology using the Danish versions of HADS and Impact of Event Scale – revised (IES-R). A cardiac nurse certified in MoCA screening did the early cognitive screening in an undisturbed room. MoCA examines the following cognitive domains: visuospatial abilities, executive functioning, memory, attention, language, and orientation.[32] The cognitive screening takes roughly 10 minutes and is scored out of 30 points, with higher scores reflecting better cognitive status. In this study we adapted the most used MoCA cut-off score of <26 to define cognitive impairment. A threshold of ≥26 is considered a normal cognitive functional level.[32] One point was added to the total score to correct for the influence of individuals with ≤12 years of education.

The survivors were asked to complete HADS and IES-R in the packet of paper PRO questionnaires. The same threshold of ≥8 for defining symptoms of anxiety and depression was chosen for this study. IES-R[111], which measures self-reported traumatic distress, contains 22 items divided into three subscales: intrusion (8 items), avoidance (8 items), and hyperarousal (6 items). The severity of each symptom is rated from 0 (not at all) to 4 (extremely), with a maximum score of 88. Higher scores indicate worse symptoms. The literature varies in terms of what IES-R threshold identifying traumatic distress is recommended. A threshold of ≥30 for defining early trauma reactions was chosen for this study.[54] IES-R has shown good internal consistency and reliability when used in cardiac patients.[51],[112]

Three-month follow-up

The three-month procedure consisted of a comprehensive neuropsychological test battery (in-hospital) (see Supplementary material, Paper 2b), and repeated collection of PROMs (HADS and IES-R) (web-based survey in addition to the paper packet). The carefully selected neuropsychological tests included: Verbal Affective Memory Task-26[113], Rey's Complex Figure[114], Letter-Number Sequencing Test from the Wechsler Adult Intelligence Scale-IV[115], and Delis-Kaplan Executive Function System tests[116], which included four tests on: trail making, verbal fluency, design fluency, and colour-word interference. Trained psychology students or a cardiac nurse carried out the session in undisturbed test facilities using a predetermined test manual. Due to COVID-19 minor modifications were made regarding the location and timing of the neuropsychological testing (Paper 2b contains more details).

Outcome measures

Assessed at the three-month follow-up, the primary cognitive outcome was the performance of neuropsychological tasks, while the primary psychopathological outcomes were HADS-A, HADS-D, and IES-R scores. We divided the cognitive outcomes into a non-favourable outcome (nFO) group and a favourable outcome (FO) group, and psychopathology into clinical levels of anxiety, depression and PTSD. The cognitive nFO was defined as performing with a standard deviation (SD) of 1.5 under the norm or reference data on at least one test or a 1.0 SD on two or more tests. Clinical levels of psychopathology were defined as HADS-A ≥8, HADS-D ≥8, or IES-R ≥30.

Data management and analysis

Seven to 10 days before the three-month follow-up, the online package of PRO measurements was sent by e-mail to participants. The questionnaire was designed and administered through a secured online survey system (LimeSurvey®, https://www.limesurvey.org/) using token-generated links. If the questionnaire had not been completed by the follow-up, participants had the opportunity to do so at follow-up. All outcome data was stored in LimeSurvey. Descriptive statistics were used to summarise sociodemographic, medical pre-arrest history and clinical characteristics. MoCA subscale scores were presented using box and whisker plots. Pearsons' chi-square tests and Fisher's exact tests were applied to compare baseline patient and cardiac arrest characteristics in PRO non-responders but also dropouts at follow-up with the participants. Wilcoxon rank-sum tests were used when comparing early screening results for those survivors we lost contact to at follow-up to the follow-up completers. In addition, we applied Students t-tests and Pearsons' chi-square tests to compare patients admitted in a coma and survivors admitted awake on cognitive and psychopathological measures during hospitalisation and at the three-month follow-up.

As a measure of association between the early screening results and the selected outcomes, logistic regression models (dichotomised outcomes) were applied. Results were reported as odds ratios (OR) and 95% confidence intervals (CI). All analyses were adjusted for carefully selected confounders (sex, age, admission to ICU and time to ROSC). Due to the scarcity of data available to base our calculations on, no formal power or sample size estimation was performed (Please see Study 2a). A p-value of <.05 was considered statistically significant. All data were analysed using Stata 15.1 software.

Study 3: Qualitative focus group study (Paper 3)

Study design

Study 3 was designed as a qualitative explorative interview study. Although PROMs can indisputably produce valuable information on subjective perceptions of various phenomena, they are not designed to capture an in-depth understanding of the lived experience of how OHCA survivors perceive their world. As a result face-to-face focus groups were used.

Participants, recruitment and setting

The study was carried out at REHPA in Nyborg, Denmark in November 2018 and in March 2019. Initiated by REHPA, the Danish Heart Foundation, and the Danish Cardiac Resuscitation Council network, 33 participants were purposive sampled via websites, leaflets at cardiac arrest centres in Denmark, and via the Danish Cardiac Arrest Survivorship network. Inclusion criteria were adult OHCA survivors with a self-identified need for rehabilitation who were able to do self-care and activities of daily living independently. The self-identified rehabilitation needs (distress and problems identified the previous week) were rated on the REHPA scale (formerly called the Distress Thermometer, a validated scale to assess rehabilitation needs in cancer care). A score of ≥3 determined the need for rehabilitation. Supplementary questions were added to the scale regarding problems related to known secondary mental health consequences of surviving cardiac arrest. Individuals who were unable to speak and understand Danish were excluded. The content of the REHPA rehabilitation course for cardiac arrest survivors is described in a separate article not included in this PhD.[117]

Ethical considerations

The study is registered with the Regional Committees on Health Research Ethics for Southern Denmark (20192000-66) and adheres to the Declaration of Helsinki. All participants provided written informed consent.

Data collection and sampling

Data were collected in a quiet room at the first two cardiac arrest rehabilitation courses held at REHPA. The focus groups met at the rehabilitation courses, which meant participants were familiar with one another. To ensure social recognition, group dynamics, a safe environment, and conversation throughout the focus group interview, the participants were divided into groups of four to seven according to age, sex, and family type. The first author (MKW), who is an experienced cardiac nurse, was the moderator for the interviews and the third or last author was an observer/assistant (LHT or MM). The interviews, which were scheduled to last one to one and a half hours, depending on the participants and data saturation, were carried out based on a semi-structured interview guide consisting of an introduction and open-ended questions guided by the objectives. The guide was broadened in relation to daily life after the November 2018 interviews for the March 2019 interviews and relevant prompts were used (Table 5). The six interviews were recorded and transcribed verbatim.

Table 5. Prompts used in focus groups

- Could you please talk about your concerns, and what has been most important for you after your cardiac arrest?
- Could you please talk about if and what kind of support you might have needed.from your surroundings and health professionals after your cardiac arrest?
- Could you please describe how you experienced daily life after your cardiac arrest?
- Could you please describe the impact your cardiac arrest had on your daily life?

Sociodemographic (sex, age, region of residence in Denmark, family type (living alone, living with spouse/partner or living with spouse/partner and children), implantable cardioverter defibrillator, education (elementary school, high school or college), and employment) and clinical variables (time since OHCA and its aetiology) were collected prior to the course using a self-reported questionnaire. After the interview, one male participant withdrew from the study and was excluded.

Data analysis and interpretation

A phenomenological-hermeneutical approach guided by the French philosopher Paul Ricoeur (1913–2015) guided the analysis of the transcribed interviews. Ricoeur emphasised that insight can be gained by interpreting texts and applying critical interpretation, the former consisting of three methodological phases, beginning with a *naïve reading*, where the researcher (open-mindedly) reads and re-reads the transcribed texts several times to arrive at an initial understanding of the whole. According to Ricoeur, this reading is an important first overview but only a preliminary part of the interpretation. The next phase is *structural analysis*, which involves systemising the transcribed texts into units of meaning to make further interpretations possible. This phase was carried out by identifying patterns, themes, and subthemes based on the meaning units and grouping them in relation to the research question. In practice this is a more in-depth interpretation proceeding from the naïve reading, where sentences are analysed to detect what is said and what the text is talking about. The third and last phase is *critical interpretation and discussion*, which is intended to reach further comprehensive understanding of the text, leading to a new and sophisticated understanding of the themes by including other theory or research. According to Ricoeur it becomes possible to gain a new understanding of what the lived experiences of the participants are.[118,119]

Results

In the following, a summary of the most important results from all three studies is presented. The appendices contain a more detailed description.

Results from Study 1: Cross-sectional study (Paper 1)

Of the 572 OHCA survivors hospitalised in the defined period, 491 eligible survivors were invited to participate in a national survey (Figure 4).

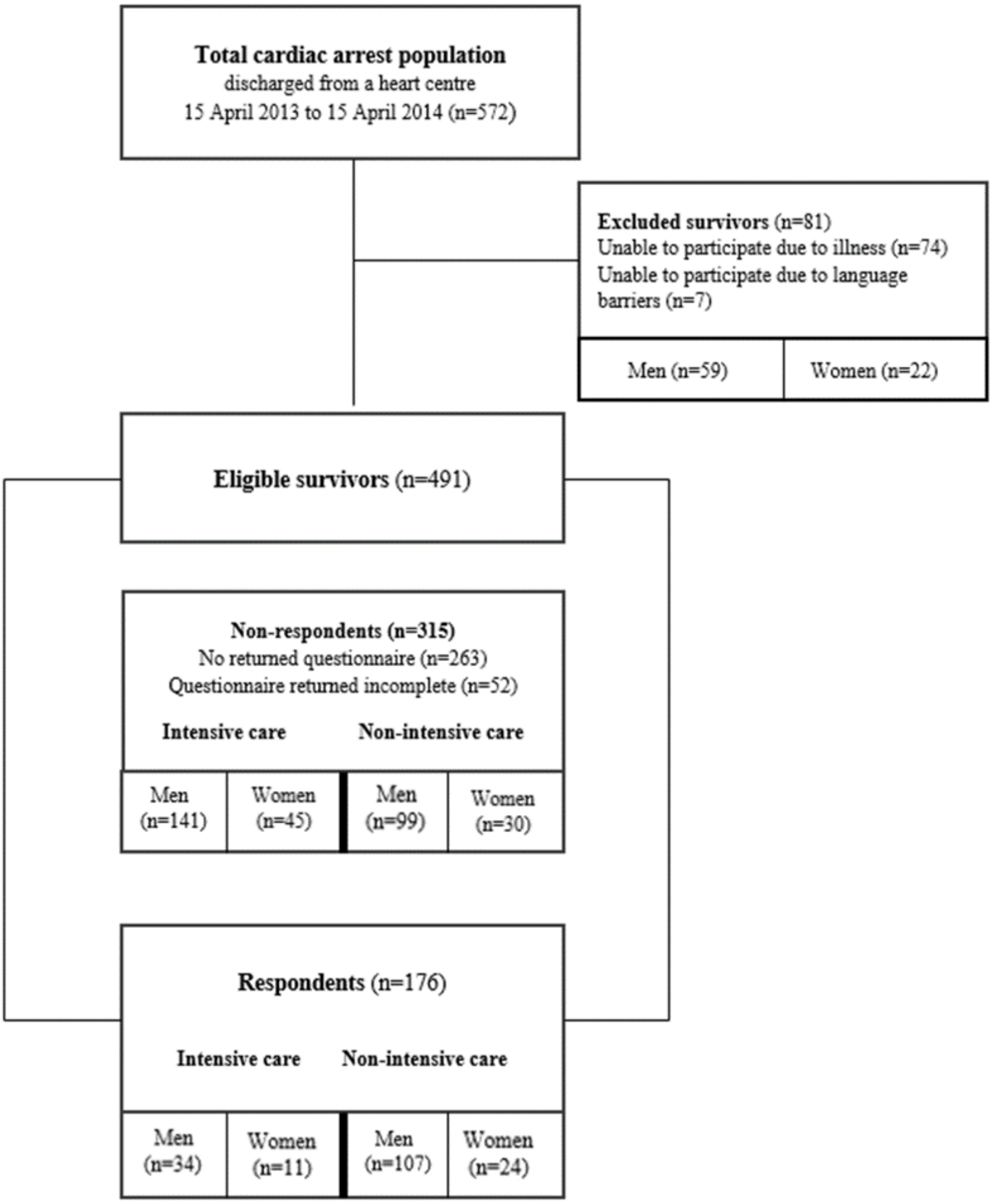


Figure 4. Patient flowchart
(Modified from Paper 1).

Participants

Of eligible survivors, 231 had been admitted to the ICU. Overall, 176 (36%) completed the questionnaire. Respondent characteristics: 80% were male, with a mean age of 59.5 years (range 20-88). Females' mean age was 52.5 years (range 21–77). ICU respondents were 19% male and 6% female, while non-ICU respondents comprised 61% male and 14% female. Male respondents were more often married (73.2% vs. 48.6%), known to have ischemic heart disease (42.3% vs. <5%), and treated with a percutaneous coronary intervention (21.1% vs. <5%) compared to female respondents.

PROs stratified by sex

Psychological distress and illness perception at hospital discharge

As depicted in Table 6, a significantly higher proportion of female respondents reported symptoms of anxiety (HADS-A ≥8) when compared to the male respondents (43% vs. 23%, p=0.04). Moreover, women reported significantly worse mean scores of illness perception (B-IPQ) on the identity item (women 4.3 (SD 3.10) vs. men 4.0 (SD 2.85), p=0.02).

Table 6. Patient-reported outcomes at hospital discharge

	All respondents n=176	Male respondents n=141	Female respondents n=35	p^a
HADS				
HADS-A, mean (SD)	5.4 (4.17)	5.1 (4.16)	6.5 (4.10)	.05
HADS-A≥8, n (%)	46 (28)	31 (23)	15 (43)	.04*
HADS-D, mean (SD)	3.6 (3.32)	3.6 (3.41)	3.5 (2.92)	.95
HADS-D≥8, n (%)	26 (16)	22 (16)	<5	.79
B-IPQ, mean (SD)				
Cognitive and emotional representations of illness				
Consequences	4.9 (2.79)	4.8 (2.85)	5.2 (2.55)	.80
Timeline	5.6 (3.42)	5.4 (3.43)	6.2 (3.39)	.40
Personal control	6.2 (3.03)	6.0 (3.12)	6.8 (2.58)	.21
Treatment control	8.6 (1.91)	8.7 (1.85)	8.4 (2.15)	.68
Identity	4.1 (2.89)	4.0 (2.85)	4.3 (3.10)	.02*
Illness concern	4.7 (3.20)	4.5 (3.11)	5.5 (3.49)	.21
Illness comprehensibility (understanding)	7.8 (2.44)	7.9 (2.31)	7.1 (2.84)	.16
Emotional response	3.9 (3.05)	3.7 (2.99)	4.9 (3.12)	.05
ESAS, mean (SD)				
Symptom distress score	20.8 (16.91)	19.8 (16.96)	24.9 (16.28)	.24
SF-12, mean (SD)				
Physical Component Summary	42.8 (10.97)	43.4 (10.46)	40.7 (12.91)	.17
Mental Component Summary	49.8 (11.31)	50.2 (11.17)	48.4 (11.98)	.42
HeartQoL, mean (SD)				
HeartQoL global	1.9 (0.83)	2.0 (0.83)	1.8 (0.82)	.19
HeartQoL physical	1.8 (0.93)	1.9 (0.92)	1.7 (0.94)	.16
HeartQoL, emotional	2.3 (0.86)	2.3 (0 83)	1.9 (0.94)	.17
Loneliness				
Feeling alone n, %				
Sometimes or often	47 (27)	34 (25)	13 (38)	.64

HADS: Hospital Anxiety and Depression Scale, **HADS-A**: HADS for symptoms of anxiety**, HADS-D:** HADS for symptoms of depression**, B-IPQ:** Brief Illness Perception Questionnaire, **ESAS:** Edmonton Symptom Assessment System, **SF-12:** Short-Form 12, **QoL**: Quality of Life, **SD**: Standard deviation.

[a] Test of statistical significance (between male and female respondents adjusted for age).

Symptom burden at hospital discharge

With respect to symptom burden, female survivors reported significantly more severe tiredness/ fatigue symptoms than their male counterparts (5.26 (SD 2.48) vs. 3.92 (SD 2.93), p=0.01) (Table 7).

Table 7. Symptom burden at hospital discharge

	All respondents n=176	**Male respondents, n=141**	**Female respondents, n=35**	**p^a**
ESAS, mean (SD), median [IQR]	20.8 (16.91) 17.0 [7-30]	19.8 (16.96) 15.0 [6-28]	24.9 (16.28) 22.0 [12-38.5]	.24
Pain	2.93 (2.77) 3.0 [1-5]	2.79 (2.78) 2.0 [0.5-5]	3.52 (2.69) 3.0 [1-6]	.06
Tiredness/ Fatigue (decreased energy level)	4.19 (2.89) 3.0 [2-7]	3.92 (2.93) 3.0 [1-7]	5.26 (2.48) 6.0 [3-7]	.01*
Nausea	0.95 (2.00) 0.0 [0-1]	0.89 (1.91) 0.0 [0-1]	1.21 (2.20) 0.0 [0-1]	.70
Drowsiness (sleepiness)	2.77 (2.66) 2.0 [0-5]	2.67 (2.67) 2.0 [0-4]	3.17 (2.61) 3.0 [1-5]	.44
Appetite	2.02 (2.58) 0.0 [0-4]	1.94 (2.58) 0.0 [0-4]	2.34 (2.59) 1.0 [0-5]	.67
Shortness of breath	2.48 (2.83) 2.0 [0-4]	2.52 (2.97) 1.0 [0-5]	2.29 (2.18) 2.0 [0-4]	.04
Depressed (blue or sad)	1.86 (2.32) 1.0 [0-3]	1.67 (2.19) 1.0 [0-3]	2.60 (2.68) 2.0 [0-4]	.05
Anxious (nervousness or restlessness)	1.80 (2.59) 0.0 [0-3]	1.66 (2.52) 0.0 [0-3]	2.34 (2.83) 2.0 [0-3]	.29
Dizziness	1.74 (2.24) 1.0 [0-3]	1.67 (2.17) 1.0 [0-3]	2.03 (2.50) 1.0 [0-4]	.63
Sensation of well-being (overall comfort, both physical and otherwise)	2.17 (2.39) 1.0 [0-4]	2.04 (2.40) 1.0 [0-3]	2.66 (2.31) 2.0 [0-5]	.28

ESAS: Edmonton Symptom Assessment System, **SD**: Standard deviation, **IQR**: Interquartile range
[a] Test of statistical significance (between male and female respondents adjusted for age).

No significant sex differences were found in either HRQoL, perceived health, or loneliness.

Results from Study 2: Prospective cohort study (Papers 2a and 2b)

Of the 665 OHCA survivors hospitalised from December 2017 to February 2022, 190 were excluded, while 475 survivors were eligible for participation, though 57 declined participation, 101 were transferred to another hospital before the opportunity arose to approach survivors, and 20 survivors exceeded the time for inclusion (Figure 5).

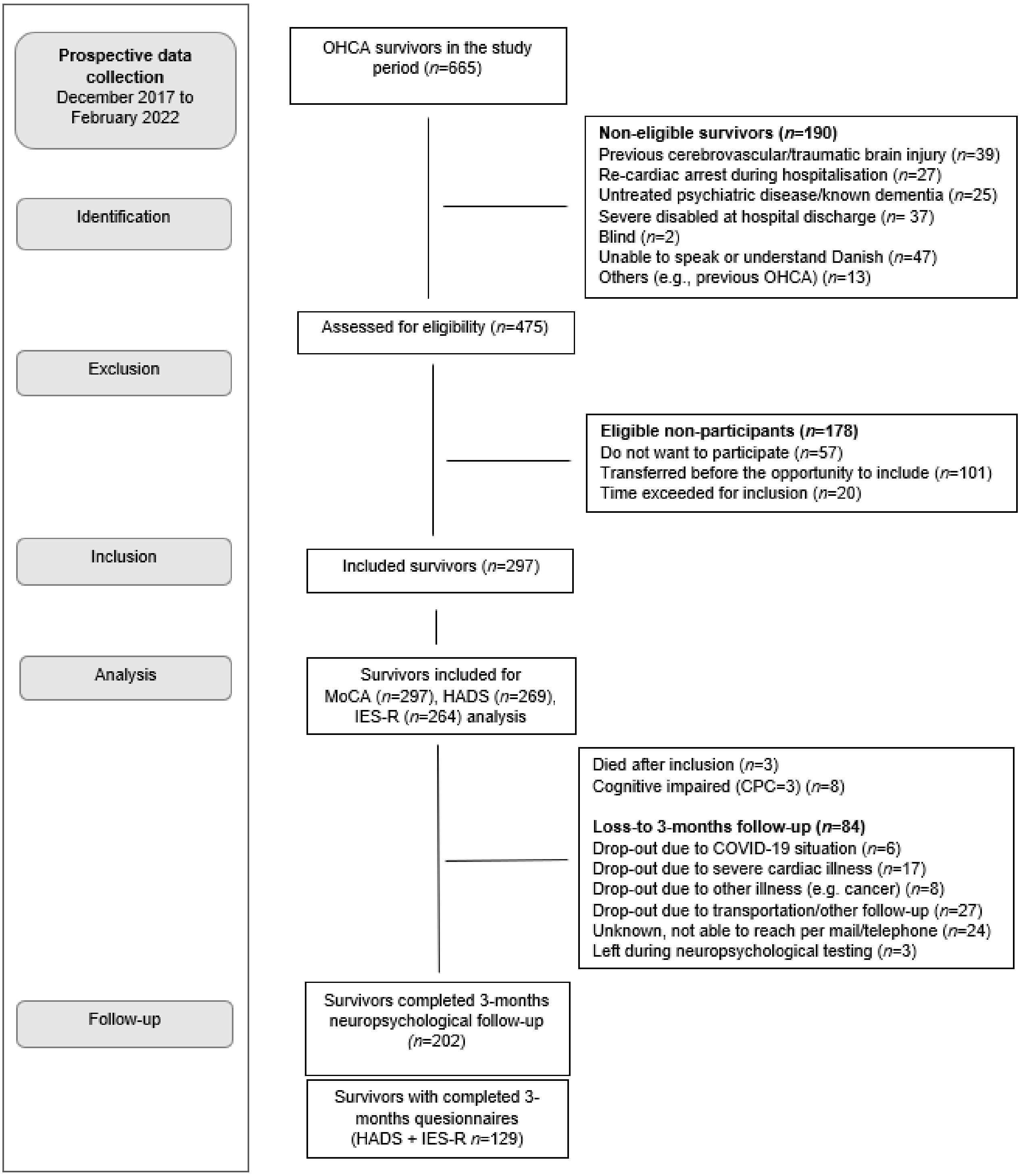


Figure 5. REVIVAL flowchart
(Adapted from Paper 2b)

OHCA: Out-of-hospital cardiac arrest, **MoCA**: Montreal Cognitive Assessment, **HADS:** Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event Scale - revised

Participants

Overall, 297 survivors (16% women) were included in the study. The baseline demographics included: median age of 59 years (interquartile range [IQR]: 50–67), 98% were Caucasian, 82% were married, 60% were working prior to cardiac arrest, and the majority (60%) had upper secondary education, vocational training, or short-cycle tertiary education (International Standard Classification of Education level 3 or 5). More than half of the cardiac arrests took place in a public place, the median time to ROSC was 10 minutes (IQR: 7–16), more than one fifth were known to have ischemic heart disease, which was the predominant cause (68%) of cardiac arrest. Approximately two-thirds were treated at the ICU (n=188), more than 60% mechanically ventilated, and the median length of admission was 12 days (IQR: 8–17).

The Screening procedure during hospitalisation

The total median MoCA score was 24 (IQR: 21–26). Overall, 65% had a MoCA total score <26. Memory, visuospatial, and executive functioning were affected most (Figure 6).

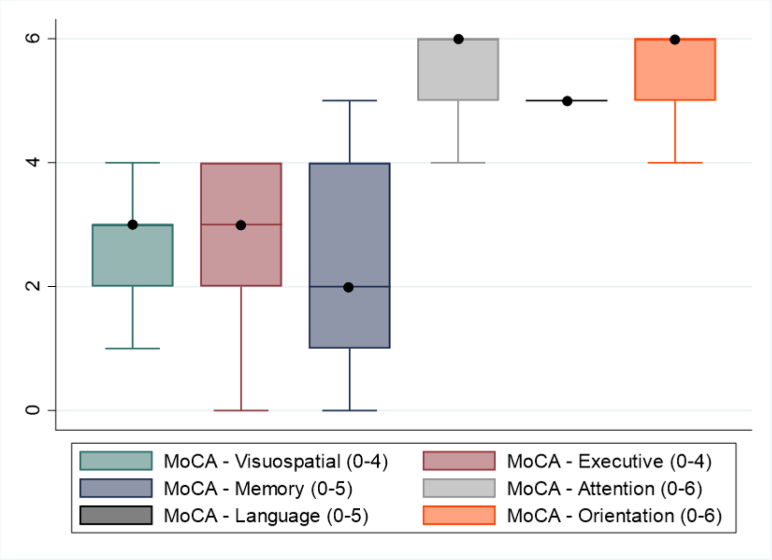


Figure 6. Cognitive screening with MoCA subdomain performance scores during hospitalisation (Adapted from Paper 2b)

MoCA: Montreal Cognitive Assessment

Compared to the MoCA ≥26 group, survivors with a MoCA score <26 were older (60 years (IQR: 61-69) vs. 57 years (IQR: 48-54), p=0.001) and had received intensive care therapy more often (p=0.001) (See Table 8).

In terms of symptoms of psychopathology, 25% of participants reported symptoms of anxiety, 20% symptoms of depression and 21% symptoms of traumatic distress (Table 8). As found in Table 8, survivors with HADS-A ≥8 had been admitted to the ICU more often when compared to survivors with HADS-A <8 (p=0.02). Moreover, survivors reporting IES-R ≥30 were younger (58 years (IQR: 47-64) vs. 60 years (IQR: 51-68), p=0.04) and with a longer time to ROSC (15 minutes (IQR: 10-20) vs. 10 (IQR: 7-15), p=0.005) when compared to survivors with IES-R <30. Non-respondents of HADS and IES-R did not differ from the respondents according to baseline patient and cardiac arrest characteristics.

Study participants at three-month follow-up

Three participants died during the follow-up period. Overall, 28% were lost to follow-up. In total, 202 survivors were neuropsychologically tested. Compared to the overall population, the tested participants were found with a higher educational level (ISCED 3-8) (84% vs. 80%, p=.01), and fewer presented with a MoCA score <26 (median 25 vs. 24, p<.001). In total, 65% of the neuropsychologically tested survivors responded to the HADS and IES-R.

Non-favorable cognitive outcome and clinical levels of psychopathology at three-month follow-up

As depicted in Table 8, a total of 53% presented with a cognitive nFO. All tested domains (memory, attention and executive functioning) were afflicted. The unconscious admitted patients were more often found with a cognitive nFO when compared to the conscious admitted survivors (54% vs. 52%, p=0.04). Overall, 17% reported clinical levels of anxiety, 15% clinical levels of depression and 19% clinical levels of PTSD.

Table 8. Differences between patients admitted unconscious and conscious on cognitive and psychopathological measures during hospitalisation and at the three-month follow-up

	Total population		**Unconscious at admission**		**Conscious at admission**		**P**[a]	**P**[b]
	T1 *n*= 297	**T2** *n*=202	**T1** *n*=188	**T2** *n*=127	**T1** *n*=109	**T2** *n*=75		
Cognition								
MoCA								
Total MoCA mean ± SD	23.3 ± 4.2	N/A	22.6 ± 4.3	N/A	24.5 ± 3.7	N/A	0.0001*	
median (IQR)	24 (21-26)		24 (20-26)		25 (23-27)			
MoCA <26, n (%)	192 (65)	N/A	135 (72)	N/A	57 (52)	N/A	0.001*	
Neuropsychological test								
Non-favorable cognitive outcome, n (%)	N/A	107 (53)	N/A	68 (54)	N/A	39 (52)		0.04*
Psychopathology								
HADS	*n*=269	*n*=129	*n*=170	*n*=78	*n*=99	*n*=51		
HADS-A mean (SD)	5.7 (3.9)	3.8 (4.0)	5.9 (3.8)	3.9 (4.0)	5.2 (3.9)	3.7 (4.0)	0.16	0.69
median (IQR)	5 (2-8)	3 (1-5)	5 (3-9)	3 (1-5)	5 (2-7)	3 (1-4)		
HADS-A ≥8, n (%)	68 (25)	22 (17)	50 (29)	15 (19)	18 (18)	7 (14)	0.02*	0.42
HADS-D mean (SD)	4.6 (3.7)	3.2 (3.8)	4.9 (3.7)	3.0 (3.8)	4.0 (3.6)	3.5 (3.7)	0.11	0.62
median (IQR)	3 (1-7)	2 (0-5)	4 (2-7)	2 (0-5)	3 (1-6.5)	2 (1-6)		
HADS-D ≥8, n (%)	53 (20)	19 (15)	37 (22)	11 (14)	16 (16)	8 (16)	0.22	0.95
IES-R	*n*=264	*n*=129	*n*=165	*n*=78	*n*=98	*n*=51		
IES-R mean (SD)	19.5 (13.7)	15.6 (15.0)	20.5 (14.7)	15.4 (15.0)	17.8 (12.0)	16.0 (15.2)	0.13	0.79
median (IQR)	17 (8-27)	10 (6-21)	18.5 (9-30)	10.5 (5-21)	16 (7.5-26)	10 (6-22)		
ES-R ≥30, n (%)	55 (21)	25 (19)	38 (25)	14 (18)	17 (18)	11 (22)	0.08	0.96

MoCA: Montreal Cognitive Assessment, **HADS-A**: Hospital Anxiety and Depression Scale – Anxiety, **HADS-D**: Hospital Anxiety and Depression Scale - Depression, **IES-R:** Impact of Event Scale – revised

a Test of T1 difference between the unconscious admitted group and the conscious admitted group. Student's t-test for continuous variables and Chi-square test for categorical variables
b Test of T2 differences between the unconscious admitted group and the conscious admitted group. Student's t-test for continuous variables and Chi-square test for categorical variables

Associations between screening results and outcomes at three-month follow-up

Those exhibiting MoCA <26 during hospitalisation had a higher odds of a cognitive nFO at three months (OR: 2.54; 95% CI: 1.43–4.51, p=0.001). An effect of age (p=0.001) was found, but no other associations with a cognitive nFO were detected. In terms of psychopathology, those reporting symptoms of anxiety during hospitalisation had a higher odds of reporting clinical levels of anxiety at three months (OR: 6.70; 2.40-18.72, p<0.001), those reporting symptoms of depression during hospitalisation had a higher odds of reporting clinical levels of depression at follow-up (OR: 4.69; 1.69-13.02, p=0.003). Moreover, associations were found between those reporting symptoms of traumatic distress during hospitalisation and those reporting clinical levels of PTSD at follow-up (OR 7.07: 2.67-18.73, $p<0.001$). Female sex was found to be a strong predictor of in particular clinical levels of anxiety and clinical levels of PTSD at three months. No other associations with clinical levels of psychopathology were found.

Findings from Study 3: Qualitative focus group study (Paper 3)

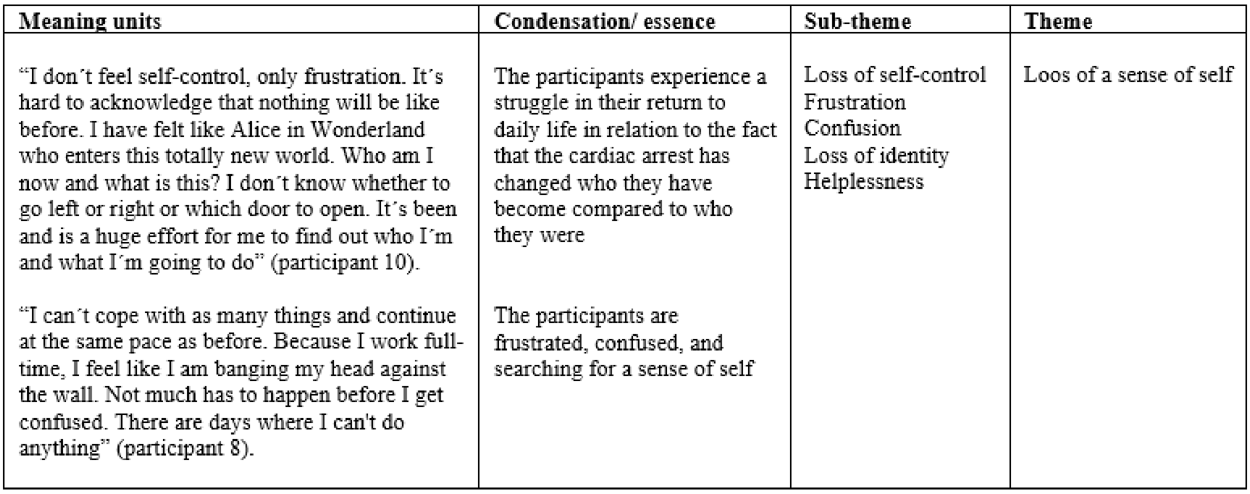
Participants

Thirty-two OHCA survivors, widely representing all regions in Denmark, participated in the six focus group interviews, 75% of whom were male, while a mean age for the entire group was 59 years, ranging from 40–83. Cardiovascular disease was the primary cause of OHCA in 66% of the interviewees. Median time since OHCA was 16 months (range 3 months to 11 years). Twenty-one participants had an implantable cardioverter defibrillator. Most participants lived with a spouse/ or partner. There was 69% who were working prior to their cardiac arrest, 53% of whom had returned to work. Nine participants were retired or on sick leave prior to their cardiac arrest, and 19% had finished college.

Narratives

The analysis of the qualitative data from the six focus group interviews led to the identification of three main narratives about the consequences the participants experienced in daily life after resuscitation: a fragmented memory while at the mercy of the system; living in the shadow of anxiety and mixed feelings; and a loss of sense of self (Table 9). In the following, the narratives and the researchers' interpretations of them will be presented.

Table 9. Example of a structural analysis
(Modified from Paper 3)



Meaning units	Condensation/ essence	Sub-theme	Theme
"I don´t feel self-control, only frustration. It´s hard to acknowledge that nothing will be like before. I have felt like Alice in Wonderland who enters this totally new world. Who am I now and what is this? I don´t know whether to go left or right or which door to open. It´s been and is a huge effort for me to find out who I´m and what I´m going to do" (participant 10).	The participants experience a struggle in their return to daily life in relation to the fact that the cardiac arrest has changed who they have become compared to who they were	Loss of self-control Frustration Confusion Loss of identity Helplessness	Loos of a sense of self
"I can´t cope with as many things and continue at the same pace as before. Because I work full-time, I feel like I am banging my head against the wall. Not much has to happen before I get confused. There are days where I can't do anything" (participant 8).	The participants are frustrated, confused, and searching for a sense of self		

Narrative 1. A fragmented memory while at the mercy of the system

The survivor narrative of a fragmented memory while at the mercy of the system encompassed how acute cardiac arrest still influenced participants' outlook on daily life. In particular, the survivors reflected on suffering fragmented amnesia about what happened before and during the arrest but also in the weeks that followed. Apart from the acute treatment and care, the other experiences were full of a mixture of sounds, colours with white light or darkness, ambience, and surroundings running at a high pace. Survivors viewed the bodily experiences of being treated while at the mercy of the system as traumatic and as having taken root in them, especially when shifting between being awake and in a chaotic state and in then experiencing nothing. Several participants expressed a mixture of feelings, e.g. frustration, lack of control and powerlessness, attaching words such as traumatic, intense, and fight to what was a frightening experience. One of the consequences of these unpleasant and overwhelming experiences was feelings that dominated the daily life narratives of participants. Many survivors nonetheless also pointed out feelings of gratitude towards their rescuers and the health care system.

Narrative 2. Living in the shadow of anxiety and mixed feelings

The survivor narrative of living in the shadow of anxiety and mixed feelings covered how most survivors struggled with persistent and overwhelming emotional reactions in daily life. They emphasised that living in the shadow of anxiety, feelings of sadness, and restlessness restricted daily life. Many expressed feeling down and caught in a black hole without joy. The consequences of these feelings meant day-to-day routines were suddenly troublesome and influenced how they coped with daily life. In particular, avoiding reminders of the cardiac arrest and not having the mental energy to socialise with the family dominated daily life. Several participants described feeling a prolonged sense of vulnerability, reflected as bodily reactions and intrusive thoughts when reminded of what happened, all of which were reactions that arose after hospital discharge. Feeling guilty towards close relatives, inadequate, and lonely were common among the participants. Particularly feelings of guilt and worry about the impact of the cardiac arrest and the illness trajectory on their closest relatives cast a shadow over their daily lives. Survivors mainly expressed these mixed feelings if a close relative had been present during resuscitation or if they were thinking about the risk of hereditary cardiac illness in their children. The importance of emotional support, from health care professionals and peers, was emphasised, though most participants said that it was lacking during their illness even though it could have helped them manage daily life better.

Narrative 3. A loss of a sense of self

The survivor narrative of a loss of a sense of self was reflected in the long-term experiences of having lost oneself after the cardiac arrest. The survivors said they struggled to hold on to normality and balancing a changed daily life. They described the difficulty of coming to the realisation that nothing would be like before, that the underlying foundation of their identity had disappeared, as well as their sense of self, not to mention the new way other pictured them. This was especially predominant in younger and middle-aged participants still on to the labour market whose work had been a substantial part of their identity. Finding acceptance among colleagues was highlighted as crucial for returning to daily life. Several survivors struggled with prolonged, extreme fatigue accompanied by difficulty concentrating, a lack of focus and mental resources, as well as short-term memory problems, headaches, and feeling irritable and irrational. These disruptive challenges affected their self-perception, which they described as losing a part of themselves and their identity, leaving them in a powerless position where they needed help in daily life. Positive experiences were also described, for example, survivors receiving support and guidance in managing the impairments they now had. Finally, they agreed that the sooner the health care system proffered a helping hand, the easier their disrupted and altered daily life would be to deal with.

Discussion

Inspired by TT, the main goal of this PhD thesis was to explore recovery and mental health after OHCA survival to provide new knowledge on post-resuscitation care and ultimately to improve current quality of care and to optimise systems of care in cardiac arrest survivorship. The TT framework was used to provide insight into the points in the cardiac arrest pathway where survivors were most likely to reach a high point of vulnerability in terms of mental health. In the following, recovery and mental health are discussed in more detail, beginning with a review of the main findings of the studies in light of existing evidence, after which the broader methodological considerations will be presented, including limitations.

Survivor recovery and mental health

Main findings

PROMS in OHCA survivors

The results from Study 1 suggested that female survivors face more psychological difficulties in the immediate recovery period than male survivors. As previously mentioned women are more prone to developing psychopathology.[120] Of particular notice we found symptoms of anxiety more prevalent in women than in men. In the study more than one in three female survivors reported possible symptoms of anxiety indicating the possible presence of a mood disorder. In a Swedish national registry study of health status and psychological stress in an in-hospital cardiac arrest population, women reported worse health status and more psychological distress than the men, which supports our findings.[121] Furthermore a large multicentre randomised controlled trial of critically ill OHCA survivors found that anxiety was three times more likely to occur among females, which also substantiate our findings.[55] In terms of PROs across cardiac diagnoses, this study adds to the existing body of literature showing that the prevalence of symptoms of anxiety in female cardiac arrest survivors is higher when compared to a DenHeart population of female patients with acute myocardial infarction.[122] One possible explanation for this is that contrary to patients with myocardial infarction, some younger OHCA survivors (in particular non-coronary cardiac arrest cases) are discharged with unexplained cardiac arrest and without an early and clear cardiac diagnosis. Illness-related uncertainty is highly difficult to cope with and contributes to poorer mental health outcomes.[123] In our study the female respondents were younger than the males.

The survey results further highlighted the higher symptom burden among the females. A main finding was high levels of fatigue, a symptom that more than half of cardiac arrest survivors report as the most prominent and long-lasting strain.[45,124] The fact that fatigue is highly associated with other somatic symptoms and psychological distress, and that individuals who experience any psychological reactions are at much higher risk of being fatigued than those who are free of psychological problems is worth considering in terms of facilitating healthy outcomes in the recovery process after OHCA. Although current clinical guidelines recommend screening for both emotional problems and fatigue after cardiac arrest, screening is inconsistently applied in clinical practice and future research in this area ranks a high priority.[74] PROMs reporting fatigue are likewise hampered by the lack of evidence base. Fatigue is associated with not returning to work in populations with cardiac arrest[45] or with other brain injuries.[125,126] Findings from Study 3 confirm that fatigue and feeling worn out limit a variety of aspects of daily life and cause suffering after cardiac arrest. Again, this was particularly the case in younger survivors. Moving forward, to reveal unmet rehabilitation needs and ease the mental health recovery process, it may be beneficial to initiate an individually tailored, comprehensive multidisciplinary rehabilitation intervention before discharge for survivors of OHCA on returning to work.[127] For example, evidence shows that mobilising resources in the early stages of a disease, particularly among patients who are younger, is most difficult at work.[128]

Although sex-based differences previously have been identified on the SF-12, with female cardiac arrest survivors reporting significantly lower physical and mental component summary scores, our study did not demonstrate sex differences in HRQoL. In the absence of a cardiac arrest survivor-specific PROM, HRQoL measures are neither sufficiently sensitive nor adequately specific to capture the complex and heterogenous nature of recovery in cardiac arrest survivorship. A recent initiative proposes a co-developmental process for PROMs targeted cardiac arrest survivors (CASHQoL).[129] The aim of this process is to help define a measure that is specific to how cardiac arrest survivors feel, function and live their lives. This is highly important as both post-cardiac arrest emotional reactions and fatigue are negatively related to QoL.[130,131] Thus, the timing of measuring HRQoL in cardiac arrest survivors is also worth considering.

Early screening procedure as markers of mental health challenges in OHCA survivors

Results from the REVIVAL cohort study (Study 2) found the proportion of cognitive impairment and symptoms of psychopathology during hospitalisation in line with previous studies. The hypothesis regarding associations between worse cognitive performance during hospitalisation and cognitive nFO at three-month follow-up, and symptoms of psychopathology during hospitalisation and clinical levels of psychopathology at three-month follow-up was confirmed. To our knowledge, the study is the largest of its kind that examines an early screening procedure during hospitalisation and that tests the associations between early signs of cognitive impairment and symptoms of psychopathology and mental health outcomes at follow-up.

As recommended by ERC ESICM we chose MoCA as a cognitive screening tool. Concise and easy to administer the tool allowed us to classify survivors into the recommended, dichotomised groups (total score: MoCA <26 vs. MoCA ≥26).[32] However, classifying REVIVAL survivors according to the originally suggested MoCA total cut-off score of 26/30 might have misplaced older and less well-educated survivors in a false positive group. In addition, cognitive impairment in our younger survivors with high pre-arrest cognitive reserve may be masked, which means the residual deficits are likely underestimated. Using the MoCA threshold of 26, a previous study by Koller et al.[37] found that using an early sequential screening procedure after cardiac arrest was feasible. Their study aligns with our results as MoCA demonstrated promising results. MoCA identified cognitive impairment on equal terms if not better than the more extensive Computer Assessment of Mild Cognitive Impairment (CAMCI) tool. Moreover, MoCA identified 100% of the survivors who did not pass the 41 Cent Test.[37] Our findings corroborate the existing resuscitation literature in that problems in memory and executive functioning domains were affected most. Also in line with the literature we also found that the domain of attention was affected at T2. Notably, however, we found minimal challenges in MoCA attention tasks (vigilance) in our cohort. The sensitivity of the selected MoCA tasks on vigilance may cause potential ceiling effects for the majority of cardiac arrest survivors with mild cognitive impairment. On the other hand we found challenges in visuospatial MoCA tasks, which few other studies have also found.[132,133] Based on a review of assessment of neurocognitive function after cardiac arrest, Blennow et al.[39] highlight that these deficits may, however, be connected to executive dysfunction, rather than being independent issues.

We chose HADS, which is recommended by ERC ESICM, and IES-R as screening tools to measure symptoms of psychopathology.[18] The recommended threshold of a score of eight or more for possible symptoms of anxiety and depression has been described in patients with cardiac diseases.[99] We found that 25% of survivors reported symptoms of anxiety and 20% of depression during hospitalisation, which was in line with Study 1 and is supported by previous research.[62] Furthermore we found that 17% had symptoms of anxiety and 15% of depression at the three-month follow-up, which is in accordance with what Lilja et al. found at their six-month follow-up using HADS.[55] One possible explanation is that they only included unconscious patients admitted to the ICU, whereas 40% of the REVIVAL cohort were admitted awake.

Although interest is increasingly shown regarding emotional reactions following OHCA, there is no specific screening tool available for traumatic distress and PTSD in this population. Since the DSM-V PTSD criteria include the hyperarousal scale, IES-R has been adopted to measure traumatic stress in various populations. Applying the tool we found that 21% of survivors reported traumatic distress during hospitalisation and 19% had clinical levels of PTSD at the three-month follow-up. A large US study (CAPD cohort) (n=184567) examined in-hospital emotional challenges after resuscitation and found similar results, with emotional reactions justifying a psychiatric diagnosis found in approximately 25% of survivors in the cohort.[134] Moreover, and in line with our results, the CAPD cohort also found female survivors (Studies 1 and 2) and younger survivors (Studies 1 and 3) with a significantly higher prevalence of mood disorders. Symptoms of depression, on the other hand, were the most commonly reported mood disorder.[134]

The best time points for assessing mental health outcomes after cardiac arrest are unknown, and discharge is not necessarily the time point that best reflects the cognitive abilities or symptoms of psychopathology in patients.[26] However, using a routine mental health screening method before discharge may help understand the unique recovery process after cardiac arrest and in making care plans that help the survivor and close relatives navigate cardiac arrest survivorship. Moulaert et al. described screening as having a positive effect.[135] The associations we found in our regression models demonstrated that there seems to be a powerful rationale to use MoCA, HADS and IES-R before survivors return home. Hence, in light of the self-reported information retrieved from HADS and IES-R it is worth considering that HADS-A focuses on symptoms related to generalised anxiety and HADS-D on symptoms relating to anhedonia, a central aspect of depression (Tables 1 and 2).[99] Still, HADS it not a diagnostic tool. Assessing a possible anxiety disorder or a depression diagnosis must be administered by a trained professional within the right time frame of the diagnosis. The same methodological considerations applies with IES-R.

Consequences of returning to daily life after OHCA survival

In Study 3 we collected qualitative data from a large number of adult OHCA survivors with a self-identified need for cardiac arrest rehabilitation. Findings were based on useful and saturated data. To the best of our knowledge, this is the first study to explore in-depth the impact of cardiac arrest on daily life after resuscitation using a theoretical approach in the intertextual interpretations.

Based on Ricoeur's phenomenological-hermeneutic approach, three main narratives shed light on the participants' lived experiences of the hospital phase, their return to daily life and the more long-term consequences after survival. Focusing chiefly on daily life and long-term consequences, our findings confirmed both survey and cohort results on reporting distinct bodily (somatic) and mental suffering. Moreover, we concluded that the impact on daily life was profound with experiences of a lost sense of self. These lived experiences predominantly appeared in younger participants still on the labour market and persisted from early on to several years after resuscitation.

Regarding mental suffering, the participants especially elaborated on feelings of guilt toward their closest relatives. Similar to Studies 1 and 2 a previous interview study of 15 survivors and their relatives[132] found that anxiety and depression were highest in survivors at discharge and decreased over the next months. That study also found that family coping and dyadic satisfaction were highest at discharge and decreased for 12 months after cardiac arrest.[132] With TT[88,89] and these findings in mind, discharge is a critical point for survivors undergoing transitions, which recognises the significance of identifying not only the most vulnerable survivors with emotional reactions before returning home but also actively involving the closest relatives. Systematically involving relatives might help ease the recovery process. Higher levels of PTSD have been reported in certain relatives of OHCA survivors[136], which raises the issue of whether routinely providing close relatives with support would be beneficial.

In terms of a lost sense of self, the participants expressed difficulty in coming to the realisation that perhaps nothing would be like it was before their cardiac arrest. The majority also talked about mental health impairments such as fatigue, memory problems and irritability, all of which disrupted daily life. They emphasised the importance of health care support at an early stage. According to TT[88,89] returning to a disease-free state might not be possible, and a premorbid level of health perhaps unattainable. This is supported by Bury, who states that 'illness interrupts the expectations and plans that individuals hold for the future'.[128] As recommended in current ERC ESICM guidelines[18], both survivors and relatives must be given information, but it is worth considering whether hospital admission might not be the most appropriate time to provide information for either the survivor or their close relatives.[26] Hence employing a transitional care strategy is proposed in light of discharging survivors who are inadequately prepared to deal with bodily impairment as secondary consequences due to resuscitation, mental suffering, and a lost sense of self in the return to daily life.[137] Doing so would potentially help minimise suffering and acknowledge that a changed life means finding a new meaning.

Methodological considerations and limitations

By using three distinct methodologies this thesis gained broad and profound insights into post-resuscitation care by exploring mental health outcomes in the early stages after the event and the consequences of surviving OHCA for daily life. However, the findings reported in Studies 1–3 should be considered in the context of some important methodological considerations. The next section presents a discussion of the study methods and how their strengths and limitations may potentially have affected the results.

Due to the methodological study designs of the included studies, conclusions on causal mechanisms are not possible, only associations (Study 2). The original DenHeart study presented a nationwide survey conducted at discharge. One of the strengths of a cross-sectional design is the possibility of obtaining a great deal of (self-reported) information at one time point for a large number of subjects. However, as OHCA survivors are still a rare disease population, the risk of small samples is present. Study 1 comprised n=176 OHCA survivors (n=35 females), with a 36% response rate, potentially leading to selection bias. In addition the most critical ill survivors were ruled out. Therefore, the magnitude of difference between responders and non-responders may likely have affected the results, and it is not possible to conclude that worse PRO data resulted from being a female survivor. Still, as our results align with the existing body of literature it cannot be ruled out that female survivors need special attention regarding their mental health status before discharge from hospital to ease their recovery process.

A clear strength of Study 2 was that we prospectively included a large cohort of survivors from three highly specialised cardiac arrest centres in Denmark, which increases the generalisability of our results to the overall OHCA population. Moreover, we used standardised measurement tools. However, due to the acute hospitalisation of cardiac arrest survivors we were unable to assess pre-arrest cognitive function, though residual confounding of pre-arrest cognitive function is possible. This is a disadvantage. Moreover, we did not select a matched control group, e.g. patients hospitalised with ST-segment–elevation myocardial infarction with a similar care path who had never suffered cardiac arrest. This emphasises that our results should be approached with caution until further screening studies are conducted. Strict exclusion criteria were adopted. As a consequence the cohort might not be representative of the OHCA population, reducing the external validity of our results. On the other hand, when excluding survivors with a history of cerebrovascular or traumatic brain injury and those suffering from a serious untreatable somatic or psychiatric disease, we sought to minimise confounding factors to help answer our research questions.

As mentioned, we were unable to conclude any causal relationships. Since cognitive impairment and particularly depression share some of the same symptoms[66], it is not possible to know whether survivors presented with depressive symptoms subsequent to the onset of the cognitive impairment or if the cognitive impairment increased due to depressive symptoms. Another limitation of Study 2 is that there is no description of how HADS[99] and IES-R were translated from English into Danish, which means it is unclear whether the translations followed steps to ensure cross-cultural validity. The outcomes of interest in Study 2 were a non-favourable cognitive outcome and clinical levels of psychopathology. Data were collected through neuropsychological testing and via self-reported questionnaires. It is well-known that studies investigating neurocognitive function often are highly influenced by missing data.[39] Our study revealed that 28% were lost-to-follow-up and not randomly missing. Follow-up completers had a higher level of education and fewer exhibited a MoCA score <26 when compared to the overall population. Although missing data is common, the fact that it does not occur at random may introduce selection bias and limit the applicability of findings to the most critical ill and vulnerable survivors.

In Study 3 we chose focus group interviewing to create inductive reasoning with in-depth insights, collecting rich data, understanding the survivors experiences attempting to conduct a trustworthy structural analysis. Dependability, confirmability, transferability, and credibility were considered and described.[138] However, a possible limitation is if findings are transferrable to other contexts and cultures. In the Study 3 participants signed up for the cardiac arrest rehabilitation course with a self-identified need for rehabilitation. Consequently one could postulate that the findings were heavily influenced by cardiac arrest survivors struggling to overcome the effects of the disruptive cardiac arrest to re-establish a meaningful life. It is plausible that the findings reflect the most vulnerable survivors who have not succeed in making a healthy transition. For several cardiac arrest survivors the recovery process is rapid and easy, mental health challenges are not an issue and the impact on daily life inconsequential. Furthermore, it is likely that the participants experienced an increased awareness of the consequences of the cardiac arrest survivorship while participating in the course. Thus, in voicing the experiences of the most vulnerable survivors, it is vital to improve quality of care for those in need of support and rehabilitation. According to Ricoeur, preunderstanding of the first author regarding the survivors and research topic allows to explore the topic further and deeper, carefully balancing what is already believed with what new might be learned. However, in order to avoid establishing a horizon fixed beforehand, thus making it possible to be true to the requirement of openness toward what patients talked about, the moderator who has no a priori knowledge of this patient group or research topic participated in the conduct of the analysis and interpretation.

Overall, the study samples predominantly comprised males, and the small percentage of females may have affected the findings. This is in particular of importance in Study 1. However, in all three studies the distribution between men and women represents a real-life picture of this population since male OHCA survivors represent the vast majority (about 80%) of OHCA survivors.

Conclusion

In conclusion, current knowledge on recovery and mental health after cardiac arrest survival concerning immediate recovery, early markers of long-term outcomes and impact on daily life is limited. Knowledge gaps exist in terms of early needs assessment identifying mental health challenges post-cardiac arrest before discharge. Our findings in Studies 1–3 indicate that hospital discharge is an especially vulnerable time point in terms of mental health for OHCA survivors and that the recovery process can be experienced as complex in the absence of proper transitional care and support in those survivors at risk of not making healthy transitions after cardiac arrest. The main conclusions of this thesis are:

- Female survivors of cardiac arrest reported worse PROs, e.g. psychological distress (anxiety symptoms) and higher symptom burden (symptoms of fatigue) in the immediate recovery period after resuscitation compared to male survivors. Attention should focus on early symptom screening at hospital discharge to identify those in need of targeted psychological support and rehabilitation.
- Most survivors exhibited cognitive impairment and symptoms of psychopathology during hospitalisation that were associated with non-favourable mental health outcomes at the three-month follow-up, emphasising the need for routine screening of cognitive impairment and symptoms of psychopathology during hospitalisation using MoCA, HADS and IES–R to identify the most vulnerable survivors.
- The prevailing lived experiences of the impact of surviving cardiac arrest on daily life were distinct bodily impairments, mental suffering and a loss of sense of self from early on to several years after resuscitation. There appears to be an urgent need to address emotional reactions and to initiate transitional care programmes early after cardiac arrest to address and identify care needs, particularly among younger survivors still on the labour market.
- Overall, future intervention trials are required to provide additional evidence to support these findings.

Future perspectives

Clinical implications

Although more people are expected to survive OHCA in the future, knowledge gaps exist in terms of identifying secondary mental health challenges at an early stage after cardiac arrest survival. Implementing screening practices at discharge is recommended. In line with these recommendations, this thesis also found that an early, systematic and clinical mental health screening approach comprising of at least MoCA, HADS and IES-R is recommendable for all cardiac arrest survivors in daily practice. Although screening tools generally only require little training and practice, and are usually easy to implement, often at low cost, Denmark does not currently have a recommended approach to clinical screening. Without this, the transitions that take place in the OHCA trajectory remain somewhat opaque in their complexity. If discharge planning is comprehensive, e.g. for the risk groups identified in this thesis, a minimum screening approach might not be able to stand alone and may require re-screening and a multidisciplinary team approach that includes, e.g. occupational therapists[1] or other trained health care professionals.

Traditionally, cardiology and neurological specialties do not cooperate on discharge planning for this patient group.[84] However, cardiac arrest survivors are a heterogeneous population that would likely benefit from the identification of cardiac and neurological challenges before discharge. Moreover, as a vital link between these two specialities, it would be recommendable to incorporate a coordinating transitional care strategy for cardiac arrest between various providers and settings. The overall aim of this would be to facilitate healthy transitions by helping to re-define meaning, ease possible suffering, modify expectations, restructure daily life routines and develop patient and staff knowledge and skills.[90,140]

To our knowledge no standard transitional care strategies exist for OHCA survivors.[137] Adequately addressing the clinical implications of this may involve using specialised nurses who promote screening for early cognitive and emotional problems, provide information and support, support self-management and refer to specialised care when needed, as previous research shows that they were able to improve outcomes (emotional state, including symptoms of anxiety and quality of life) in cardiac arrest survivors.[135] In-hospital stays, however, may not be the ideal time or place to provide comprehensive information.[26] A stepped care approach might be useful. Additionally, including and partnering with the nearest family should be an essential part of this transitional strategy, however, as better mental health among close family members improves the care and support they give the survivor.

Research implications

The findings in this thesis have urgent future research implications. As mentioned AHA recently emphasised the importance of recovery and survivorship for resuscitation outcomes by adding recovery as the sixth link in the chain of survival.[139] Hence, to reinforce this particular link, future resuscitation research based on large-scale well-designed studies are needed to clarify which mental health tools are useful and valid measures of cognition and psychopathology including fatigue.

To provide OHCA survivors with better patient-centred care, collecting data on the symptom burden of survivors using PROs in the course of their illness trajectory is crucial. In addition the sex differences in PROs found in Study 1 should be addressed further in well-powered future studies to detect sex differences with the overall aim of improving quality of care for all OHCA survivors. However, it is worth considering that, even if we measure PROs, it will not be possible to say anything about, e.g. the biological mechanisms that causes the differences. Thus, the results from Studies 1 and 2 underline the potential of using PROMs to guide transitions of care before discharge. Incorporating PROMs in discharge planning can serve to advance our understanding of the individual survivor but can also provide differentiated care and treatment e.g. between the most severe critical ill admitted in coma versus the awake survivors. Hence, to create a robust evidence base on the use of PROMs in the early, in-hospital post-cardiac arrest recovery period, conducting additional PRO validation studies is imperative.

Despite the importance of prospective observational studies like Study 2 adding valuable data on mental health assessments exploring potential associations, future studies need to be designed as clinical, randomised controlled intervention trials investigating cause-effect relationships between an intervention and outcome, e.g. in a given treatment for preventing cognitive impairment but also targeting rehabilitation for these frequently invisible impairments. Novel knowledge in this area is desperately needed. The risk of acquired cognitive impairment and psychopathology is poorly understood. Therefore, in particular, obtaining new knowledge on modifiable factors of these challenges is warranted. Given the findings in Study 3, a future intervention targeting the whole family with a focus on QoL should also be considered. Though with the parallel collection of qualitative and quantitative data exploring dyadic coping and family life after cardiac arrest.

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Appendices

Papers 1-3

Related scientific contributions during the PhD programme

Paper 1

Sex Differences in Patient-Reported Outcomes in the Immediate Recovery Period After Resuscitation: Findings From the Cross-sectional DenHeart Survey

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Sex Differences in Patient-Reported Outcomes in the Immediate Recovery Period After Resuscitation: Findings From the Cross-sectional DenHeart Survey

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Background: A paucity of resuscitation studies have examined sex differences in patient-reported outcomes upon hospital discharge. It remains unclear whether male and female patients differ in health outcomes in their immediate responses to trauma and treatment after resuscitation. **Objectives:** The aim of this study was to examine sex differences in patient-reported outcomes in the immediate recovery period after resuscitation. **Methods:** In a national cross-sectional survey, patient-reported outcomes were measured by 5 instruments: symptoms of anxiety and depression (Hospital Anxiety and Depression Scale), illness perception (Brief Illness Perception Questionnaire [B-IPQ]), symptom burden (Edmonton Symptom Assessment Scale [ESAS]), quality of life (Heart Quality of Life Questionnaire), and perceived health status (12-Item Short Form Survey). **Results:** Of 491 eligible survivors of cardiac arrest, 176 (80% men) participated. Compared with men, resuscitated women reported worse symptoms of anxiety (Hospital Anxiety and Depression Scale–Anxiety score ≥8) (43% vs 23%; $P = .04$), emotional responses (B-IPQ) (mean [SD], 4.9 [3.12] vs 3.7 [2.99]; $P = .05$), identity (B-IPQ) (mean [SD], 4.3 [3.10] vs 4.0 [2.85]; $P = .04$),

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fatigue (ESAS) (mean [SD], 5.26 [2.48] vs 3.92 [2.93]; $P = .01$), and depressive symptoms (ESAS) (mean [SD], 2.60 [2.68] vs 1.67 [2.19]; $P = .05$). **Conclusions:** Between sexes, female survivors of cardiac arrest reported worse psychological distress and illness perception and higher symptom burden in the immediate recovery period after resuscitation. Attention should focus on early symptom screening at hospital discharge to identify those in need of targeted psychological support and rehabilitation.

KEY WORDS: health survey, patient-reported outcomes, sex differences, sudden cardiac arrest

A substantial number of survivors of sudden cardiac arrest experience short- and long-term consequences on daily life during their recovery after resuscitation.[1] One of the most prevalent postarrest challenges is psychopathological manifestations.[2] According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, psychopathology is defined as "a behavioral or psychological syndrome or pattern that occurs in an individual."[3]

Although survival rates are increasing,[4,5] sudden cardiac arrest continues to be an important public health issue.[6] The annual estimated incidence of out-of-hospital cardiac arrest lies between 67 and 170 per 100 000 individuals in Europe.[7] Compared with women, men have a 3-fold risk of cardiac arrest across all age groups. However, female individuals who had a cardiac arrest are older, have more comorbidities, have fewer initial shockable rhythms, and receive less prehospital resuscitation efforts than male cardiac arrest individuals.[8,9] The reasons for the lower cardiopulmonary resuscitation attempts in women are suggested to be caused by fewer witnessed arrests, as elderly women often live alone, and by cultural barriers, for example, removing clothes from a woman's upper chest area.[8] Although controversial,[10] most previous resuscitation studies find that female patients experience higher mortality.[11,12] Moreover, octogenarians have been found to have lower odds of being successfully resuscitated.[13] Growing research demonstrate that men and women differ in susceptibility to common diseases and response to treatment. Literature suggests that to understand the complexity of and nuance in health outcomes, knowledge from male-female health differences has to be considered to improve human health and avoid detrimental health outcomes and high health costs.[14]

Psychopathology seems to increase the risk of cardiovascular death in patients with established heart diseases.[15] Moreover, psychopathology negatively affects the level of daily functioning and health-related quality of life (HRQoL) and prevents survivors of cardiac arrest from returning to previous social roles.[2,16–18] This is particularly observed among patients who were comatose during hospital management.[19,20] Female survivors report significantly more prolonged anxiety,[21] depressive mood,[22] and posttraumatic stress disorder than male survivors do.[23,24] In addition, women report poorer functional recovery and HRQoL after out-of-hospital cardiac arrest.[25] Still, Bosson et al[24] have reported that women receive less postarrest interventions. A recent study found that the presence of self-reported acute traumatic stress upon hospital discharge is strongly associated with posttraumatic stress disorder up to 1 year after survival. In addition, these trauma reactions were more prevalent in female than male survivors.[26] Evidence to inform how and when to screen for postarrest psychological distress and symptom burden at hospital discharge is scarce.[7]

A recent scientific statement on the sudden cardiac arrest survivorship suggests including more somatic symptoms on affective domains at hospital discharge.[27] Moreover, it remains unclear whether male and female survivors differ in health outcomes in their immediate responses to trauma and treatment after resuscitation.[28] To bridge and optimize the gap between clinician-based understanding and patient experience, patient-reported outcomes (PROs) are beneficial when collecting important information about the subjective burden of postarrest symptoms and the impact of resuscitation and concomitant treatment.[29] Therefore, in an era of patient-centered care, the aim of this study was to examine sex differences in illness perception, symptom burden, anxiety, depression, HRQoL, and perceived health status in the immediate recovery period after resuscitation.

Methods

Study Design, Setting, and Patient Sample

Data were derived from the national cross-sectional DenHeart survey investigating PROs regarding health among cardiac patients at hospital discharge. The design of the original DenHeart study has been described previously in a detailed study protocol.[30] All included patients in the DenHeart study were discharged from 1 of 5 heart centers in Denmark in the period April 15, 2013, to April 15, 2014. Before leaving the hospital, all eligible patients were recruited and asked to complete a self-administrated questionnaire. If not possible, the patients were asked to complete the questionnaire within 3 days after discharge and return it by mail within 4 weeks postdischarge. Exclusion criteria were being younger than 18 years, having no Danish civil registration number, and not understanding Danish. The study population was restricted to include survivors of cardiac arrest discharged with a presumed favorable neurocognitive outcome defined as Cerebral Performance Category (CPC) scores 1 or 2 on the Glasgow-Pittsburgh

CPC and thereby expected to be able to report PROs.[31] Eligible patients were identified by diagnosis (International Classification of Diseases-10; A and B diagnosis) and a cardiac arrest diagnosis (I46). Associated codes were included: cardiac arrest without specification (I46.9), cardiac arrest with successful resuscitation (I46.0), and ventricular fibrillation (I49.0B). Study reporting follows the STROBE Statement for cross-sectional studies (www.strobe-statement.org).

Data Sources and Variables

Register Data

Information on sociodemographic variables were obtained via the following national registers: the Danish Civil Registration System,[32] the Danish National Patient Register,[33] and the Danish Education Registers.[34] Demographic characteristics (eg, sex, age, and the highest level of highest completed education) were collected from the Danish Civil Registration System and the Danish Education Registers. Level of comorbidity was collected from the Danish National Patient Register[33] and was based on the Tu Comorbidity Index score.[35] This score included the following diseases: congestive heart failure, cardiogenic shock, arrhythmia, pulmonary edema, malignancy, diabetes, cerebrovascular disease, acute/chronic renal failure, and chronic obstructive pulmonary disease, and was calculated 10 years back.[35]

Clinical Variables

Clinical data were obtained from a database in The Danish Clinical Quality Program–National Clinical Registry: the Danish Intensive Care Database.[36] Quality indicators obtained from the Danish Intensive Care Database were length of intensive care unit (ICU) admission and the following treatment variables: mechanically ventilated, length of time on ventilator, in a state of septic shock, and organ supportive treatments as use of inotropic agents.[36]

Patient-Reported Outcomes

The PROs in this study were assessed using the following 5 questionnaires.

Hospital Anxiety and Depression Scale

Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS).[37] The HADS consists of two 7-item subscales measuring symptoms of anxiety and symptoms of depression for the past week, respectively. This standardized questionnaire is designed to assess mood disorders in non-psychiatric populations. The highest possible score for each subscale is 21, with higher scores representing more psychological distress. The scale is used with a cut-off score of 8 or higher, indicating the presence of anxiety and/or depression. The validity and reliability of the HADS are good, with a mean Cronbach's α of 0.83 and 0.82 for the HADS-A and HADS-D, respectively.[38]

Brief Illness Perception Questionnaire

The Brief Illness Perception Questionnaire (B-IPQ)[38] was used to assess current cognitive and emotional representations of illness on the basis of 8 items. Five items assess cognitive illness representations: consequences (item 1), timeline (item 2), personal control (item 3), treatment control (item 4), and identity (item 5). Two items assess emotional illness representations: illness concern (item 6) and emotional response (item 8). One item assesses illness comprehensibility (understanding) (item 7). All of the items are rated using a 0 to 10 rating scale. Higher scores on items 1, 2, 5, 6, and 8 reflect a more threatening view of illness. In contrast, lower scores on items 3, 4, and 7 reflect a higher perceived threat associated with the condition. The B-IPQ has good reliability and has shown good predictive validity among patients recovering from myocardial infarction.[39]

Edmonton Symptom Assessment Scale

The Edmonton Symptom Assessment Scale (ESAS)[40] was administered to assess current symptom burden. It is a 10-item questionnaire that allows patients to rate symptoms of pain, tiredness/fatigue (decreased energy level), nausea, drowsiness (sleepiness), appetite, shortness of breath, depression (blue or sad), anxiety (nervousness or restlessness), dizziness, and sensation of well-being (overall comfort, both physical and otherwise) on a visual numeric scale. Higher scores indicate the presence and intensity of the symptoms. Although not validated in cardiac populations, ESAS is widely used for symptom assessment in clinical and research settings and is a validated instrument used in different populations of cancer patients.[40]

Heart Quality of Life Questionnaire

The validated ischemic heart disease questionnaire Heart Quality of Life Questionnaire (HeartQoL)[41,42] was administered to assess disease-specific HRQoL. The 14 items in the HeartQoL scale cluster as a bidimensional questionnaire with a 10-item HeartQoL physical subscale and a 4-item HeartQoL emotional subscale providing a global assessment and evaluation of how much a patient is bothered with their heart disease within the previous 4 weeks. The answer options range from 0 to 3 (poor to better HRQoL), with higher scores indicating better HRQoL status. The Danish HeartQoL questionnaire has demonstrated satisfactory psychometric attributes of validity and reliability in recipients of implantable cardioverter defibrillator.[43]

12-Item Short Form Survey

The 12-Item Short Form Survey (SF-12) is a generic 12-item questionnaire measure of overall health divided into 2 components, the physical component summary score (PCS) and the mental component summary score (MCS).[44] The component scores are calculated to summarize physical and mental functioning, respectively.

The patients estimate their health during the past 4 weeks. Cronbach's α values of 0.87 and 0.84 for PCS-12 and MCS-12, respectively, have been reported in a population of coronary heart disease patients. Moreover, SF-12 is found as a useful measure of HRQoL in survivors of out-of-hospital cardiac arrest[45] and is claimed with acceptable evidence to discriminate between men and women.[46]

Ancillary Questions

Information on health behavior, such as body weight and height, smoking habits, and use of alcohol, were only obtained via the questionnaire. Body weight and height were used to assess body mass index. Alcohol intake was assessed by a beverage-specific question asking for the number of standard drinks for each day in a typical week. One standard drink contains 12 g of pure alcohol. Moreover, 1 ancillary question on loneliness was included in these analyses: "Does it ever happen that you are alone, even though you would prefer to be with other people?"

Statistical Methods

Descriptive statistics are reported as mean values and standard deviation (SD), numbers and percentages, or median and interquartile range as indicated. Comparisons between men and women in PROs (HADS, B-IPQ, ESAS, HeartQoL, and SF-12) and loneliness upon hospital discharge were carried out using Students *t* tests, Pearson χ^2 test, and Fisher Exact test where appropriate. Linear and logistic regression models were used to calculate age-adjusted *P* values for continuous and binary outcomes, respectively. All statistical analyses were conducted using STATA 15.1 (StataCorp, 2017; Stata Statistical Software: Release 15, StataCorp LLC, College Station, Texas). An α level of 0.05 was considered the threshold for statistical significance.

Ethics

The DenHeart study was approved by the institutional boards of the participating heart centers and complies with the principles outlined in the Declaration of Helsinki. The Danish Protection Agency approved the handling of data (reg. 2007-58-0015/30-0937) and is registered at ClinicalTrials.gov (NCT01926145). All patients provided informed consent based on both oral and written study information.

Results

Patient Characteristics in Relation to Sex

The population comprised a total of 491 eligible survivors of cardiac arrest with a favorable outcome (CPC score ≤2) treated at and discharged from a heart center (Figure). In all, 381 (78%) were men and 110 were

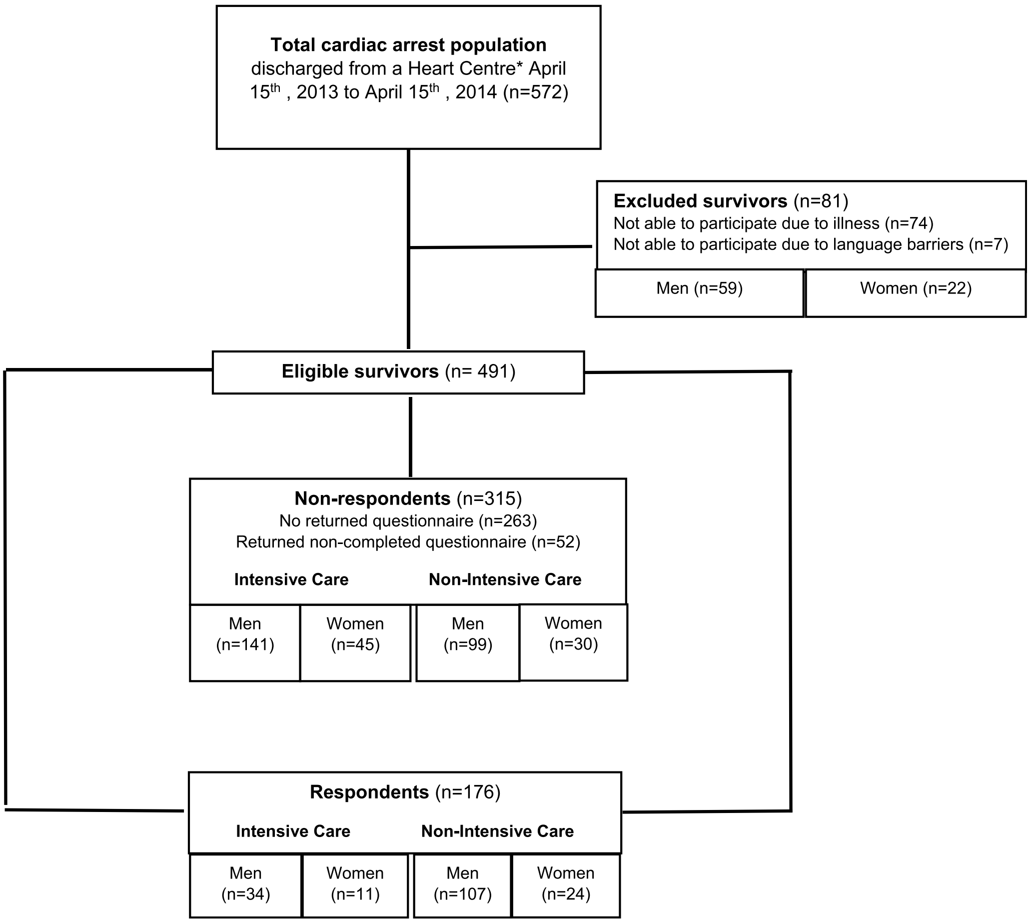

FIGURE. *Patient flowchart.*

women. Because of organ failure, 231 patients (175 men [76%] and 56 women) were admitted to and treated at the ICU. During the ICU admission, more than 90% were mechanically ventilated for a range between 1 and 9 days, and 89% were treated with inotropic agents. Of eligible survivors, approximately 60% (for both men and women) were treated in the ICU. Table 1 summarizes sociodemographic and clinical variables for the total population (respondents vs nonrespondents) stratified by sex.

As shown in the flowchart (Figure), 176 respondents completed the questionnaire. Most of the surveys were completed just upon hospital discharge. Most respondents were men (80%). The overall response rate was 36%. The male ICU respondents comprised 19% and the female ICU respondents comprised 6%, whereas the response rate among those treated at non-ICUs was 61% for men and 14% for women. Compared with the female respondents, male respondents were significantly older (mean, 59.5 vs 52.7 years; $P = .01$), more likely to be married (73% vs 49%; $P = .02$), and more often known to have ischemic heart disease (42% vs 9%; $P = <.001$), and approximately one-fifth had previously been treated with percutaneous coronary intervention, against less than 5%.

As shown in Tables 2 and 3, the female survivors were more likely to report negative consequences and worse PROs upon hospital discharge than the male survivors.

Psychological Distress and Illness Perception at Hospital Discharge—Stratified by Sex

Table 2 shows that a significantly higher proportion of the women experienced symptoms of anxiety, defined as HADS-A score of 8 or higher, compared with the men (43% vs 23%; $P = .04$). Moreover, a tendency toward a significant difference between sexes was found on the B-IPQ subscale *emotional responses*: 4.9 (SD, 3.12) versus 3.7 (SD, 2.99) ($P = .05$), with the female survivors being more likely to report negative emotional reactions such as fear, anger, and distress. On the subscale *identity*, the women also reported the number of symptoms experienced as part of surviving cardiac arrest more extensive and challenging when

TABLE 1 Sex Stratified Sociodemographic and Clinical Characteristics of Cardiac Arrest Nonrespondents Versus Respondents

	Eligible Cardiac Arrest Population						
	Men			Women			
	Nonrespondents (n = 240)	Respondents (n = 141)	P_a	Nonrespondents (n = 75)	Respondents (n = 35)	P_a	P_b
Age, mean (range), y	64.3 (18–94)	59.5 (20–88)	.17	59.8 (18–91)	52.7 (21–77)	.89	.01
Married, n (%)	143 (59.6)	104 (73.2)	.02	36 (48.0)	17 (48.6)	.26	.02
Hospital length of stay, mean (range), days	7 (1–161)	6 (1–32)	.70	7 (1–33)	8 (1–27)	.11	.12
Highest completed education, n (%)							
Basic school or no information	89 (37.1)	33 (23.2)	.08	33 (44.0)	13 (37.2)	.29	.15
Upper secondary or vocational school	112 (46.7)	75 (52.8)		27 (36.0)	14 (40.0)		
Higher education	39 (16.3)	34 (23.9)		15 (20.0)	8 (22.9)		
Intensive care unit treatment, n (%)	141 (58.8)	34 (23.9)	<.001	45 (60.0)	11 (31.4)	.01	.36
Comorbidities *10 years back,* n (%)							
Known ischemic heart disease	89 (37.1)	60 (42.3)	.32	11 (14.7)	<5	.54	<.001
Arterial hypertension	71 (29.6)	35 (25.4)	.37	25 (33.3)	5 (14.3)	.04	.17
Ventricular arrhythmia	40 (16.7)	51 (35.9)	<.001	12 (16.0)	13 (37.1)	.01	.89
Heart failure	68 (28.3)	37 (26.1)	.63	13 (17.3)	10 (28.6)	.18	.76
Previous PCI	38 (15.3)	30 (21.1)	.19	<5	<5	.56	.01
Previous CABG	7 (2.9)	19 (13.4)	<.001	<5	<5	.95	.08
COPD	17 (7.1)	7 (4.9)	.40	17 (22.7)	<5	.20	.23
Tu-Comorbidity score, n (%)							
0	98 (40.8)	55 (38.7)	.37	36 (48.0)	11 (31.4)	.05	.61
1	58 (24.2)	45 (31.7)		15 (20.0)	11 (31.4)		
≥2	84 (35.1)	44 (29.6)		24 (32.0)	13 (37.2)		
Health behavior, n (%)							
BMI ≥25	N/A	89 (66.4)		N/A	20 (64.5)		.84
BMI ≥30	N/A	33 (24.6)		N/A	8 (25.8)		.89
Smoking 15 cigarettes or more per day	N/A	17 (12.0)		N/A	<5		.77
High alcohol intake[a]	N/A	8 (7.0)		N/A	<5		.71

P_a: test of statistical significance (between nonrespondents and respondents).

P_b: test of statistical significance (between male and female respondents).

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; BMI, body mass index.

[a] The Danish Health Authority defines the high risk limit for alcohol consumption as a weekly intake of more than 21 standard drinks for men and more than 14 standard drinks for women.

TABLE 2 Patient-Reported Outcomes Among Male and Female Respondents at Hospital Discharge

	All Respondents (n = 176)	Male Respondents (n = 141)	Female Respondents (n = 35)	*P*[a]
HADS				
HADS-A, mean (SD)	5.4 (4.17)	5.1 (4.16)	6.5 (4.10)	.05
HADS-A ≥8, n (%)	46 (28)	31 (23)	15 (43)	.04
HADS-D, mean (SD)	3.6 (3.32)	3.6 (3.41)	3.5 (2.92)	.95
HADS-D ≥8, n (%)	26 (16)	22 (16)	<5	.79
B-IPQ, mean (SD)				
Cognitive and emotional representations of illness				
Consequences	4.9 (2.79)	4.8 (2.85)	5.2 (2.55)	.80
Timeline	5.6 (3.42)	5.4 (3.43)	6.2 (3.39)	.40
Personal control	6.2 (3.03)	6.0 (3.12)	6.8 (2.58)	.21
Treatment control	8.6 (1.91)	8.7 (1.85)	8.4 (2.15)	.68
Identity	4.1 (2.89)	4.0 (2.85)	4.3 (3.10)	.02
Illness concern	4.7 (3.20)	4.5 (3.11)	5.5 (3.49)	.21
Illness comprehensibility (understanding)	7.8 (2.44)	7.9 (2.31)	7.1 (2.84)	.16
Emotional response	3.9 (3.05)	3.7 (2.99)	4.9 (3.12)	.05
ESAS, mean (SD)				
Symptom distress score	20.8 (16.91)	19.8 (16.96)	24.9 (16.28)	.24
SF-12, mean (SD)				
Physical component summary score (PCS)	42.8 (10.97)	43.4 (10.46)	40.7 (12.91)	.17
Mental component summary score (MCS)	49.8 (11.31)	50.2 (11.17)	48.4 (11.98)	.42
HeartQoL, mean (SD)				
HeartQoL global	1.9 (0.83)	2.0 (0.83)	1.8 (0.82)	.19
HeartQoL physical	1.8 (0.93)	1.9 (0.92)	1.7 (0.94)	.16
HeartQoL, emotional	2.3 (0.86)	2.3 (0.83)	1.9 (0.94)	.17
Loneliness, n (%)				
Feeling alone				
Sometimes or often	47 (27)	34 (25)	13 (38)	.64

Abbreviations: HADS-A, Hospital Anxiety and Depression Scale for anxiety; HADS-D, Hospital Anxiety and Depression Scale for depression; B-IPQ: Brief Illness Perception Questionnaire; ESAS, ESAS, Edmonton Symptom Assessment System; SF-12, 12-Item Short Form Survey; HeartQoL, Heart Quality of Life Questionnaire.

[a]Test of statistical significance (between male and female respondents adjusted for *age).*

compared with the men: 4.3 (SD, 3.10) versus 4.0 (SD, 2.85) (*P* = .02).

Symptom Burden at Hospital Discharge—Stratified by Sex

As found in Table 3, statistically significant sex disparities were found for symptom burden measured by the ESAS mean scores on the subscales of *tiredness/fatigue* (3.92 [SD, 2.93] vs 5.26 [SD, 2.48]; *P* = .01) and *depressed* (1.67 [SD, 2.19] vs 2.60 [SD, 2.68]; *P* = .05), with women being considerably more burdened by those symptoms than men after resuscitation.

No significant sex differences were detected in either HRQoL, perceived health, or loneliness.

TABLE 3 Symptom Burden at Hospital Discharge Among Male and Female Respondents

	All Respondents (n = 176)	Male Respondents (n = 141)	Female Respondents (n = 35)	*P*[a]
ESAS	20.8 (16.91) 17.0 [7–30]	19.8 (16.96) 15.0 [6–28]	24.9 (16.28) 22.0 [12–38.5]	.24
Pain	2.93 (2.77) 3.0 [1–5]	2.79 (2.78) 2.0 [0.5–5]	3.52 (2.69) 3.0 [1–6]	.06
Tiredness/fatigue (decreased energy level)	4.19 (2.89) 3.0 [2–7]	3.92 (2.93) 3.0 [1–7]	5.26 (2.48) 6.0 [3–7]	.01
Nausea	0.95 (2.00) 0.0 [0–1]	0.89 (1.91) 0.0 [0–1]	1.21 (2.20) 0.0 [0–1]	.70
Drowsiness (sleepiness)	2.77 (2.66) 2.0 [0–5]	2.67 (2.67) 2.0 [0–4]	3.17 (2.61) 3.0 [1–5]	.44
Appetite	2.02 (2.58) 0.0 [0–4]	1.94 (2.58) 0.0 [0–4]	2.34 (2.59) 1.0 [0–5]	.67
Shortness of breath	2.48 (2.83) 2.0 [0–4]	2.52 (2.97) 1.0 [0–5]	2.29 (2.18) 2.0 [0–4]	.04
Depressed (blue or sad)	1.86 (2.32) 1.0 [0–3]	1.67 (2.19) 1.0 [0–3]	2.60 (2.68) 2.0 [0–4]	.05
Anxious (nervousness or restlessness)	1.80 (2.59) 0.0 [0–3]	1.66 (2.52) 0.0 [0–3]	2.34 (2.83) 2.0 [0–3]	.29
Dizziness	1.74 (2.24) 1.0 [0–3]	1.67 (2.17) 1.0 [0–3]	2.03 (2.50) 1.0 [0–4]	.63
Sensation of well-being (overall comfort, both physical and otherwise)	2.17 (2.39) 1.0 [0–4]	2.04 (2.40) 1.0 [0–3]	2.66 (2.31) 2.0 [0–5]	.28

Data are mean (SD) and median [interquartile range].

Abbreviation: ESAS, Edmonton Symptom Assessment System.

[a]Test of statistical significance (between male and female respondents adjusted for *age*).

Discussion

Key Results

The current study found that men and women differ in their immediate responses to trauma and treatment after resuscitation. The female survivors of cardiac arrest tended to report worse psychological distress and illness perception and higher symptom burden at hospital discharge. In a recent scientific statement on the cardiac arrest survivorship, Sawyer et al[27] emphasize and ask: "which patients develop psychological disorders after resuscitation?" Multiple factors may affect the postarrest psychological recovery, and various explanations may exist for this.[47] Consistent with previous studies,[48–50] we found postarrest fatigue as the most prevalent patient-reported symptom and challenging problem for both resuscitated men and women upon hospital discharge. Notably, protracted fatigue has previously been described as present in approximately 70% of the survivors at 6 months and remains present in half of the survivors 1 year after the cardiac arrest.[48,51] A European study on survivors of out-of-hospital cardiac arrest found fatigue to be one of the most predictive factors for a lower participation in society and activities of everyday life.[52] In addition, fatigue seems strongly associated with both anxiety and depression.[7]

Moreover, as mentioned, a substantially higher proportion of female survivors experienced symptoms of anxiety than the male survivors. This may indicate that female survivors perceive a traumatic event such as cardiac arrest as a more stressful event compared with male survivors, with complaints at hospital discharge that include more affective components. However, it is worth noticing that epidemiological findings point out that men and women manifest disease in fundamentally different ways. Women in general are more likely to report worse psychological distress, have higher disability levels at all ages, and show more signs of psychopathology after a traumatic and stressful event compared with men.[23,53] Literature has suggested that sex-related factors such as hormonal regulation and gender-related factors such as lifestyle and stress perception are likely to influence disease perception.[54] Although it is clear that being resuscitated can have a considerable impact on health outcomes in the immediate recovery period upon hospital discharge, especially in female survivors, this study offers a basis for planning and developing future larger-scale sex-specific studies to examine the predictive value of discharge assessment of cardiac arrest survivor's postarrest distress and symptom burden on longer-term psychopathology.

Methodological Considerations and Limitations

This study included survivors of cardiac arrest from a large national cross-sectional survey. However, the study may be biased by participation bias. Compared with the non–intensive care survivors, the rather low ICU response rate among both sexes was as expected. Survivors of cardiac arrest in need of critical care often face several challenges after ICU treatment, which affect all body systems. This vulnerable group is therefore most likely not able to participate compared with the non–intensive care survivors.

Cognitive impairment after ICU treatment is a substantial problem.[20] A possible limitation of this study is that a cognitive screening to detect mild to moderate neurocognitive impairment at hospital discharge was not performed. In future studies, it is highly essential that a cognitive assessment is performed besides using clinician-reported measures such as the CPC[55] because, first, it is evident that emotional changes and development of psychopathology are common after anoxic brain damage, and second, the 5-point CPC scale has been criticized for being too crude and insensitive to detect cognitive impairment after resuscitation.[27]

We did not reach significant differences in several health outcomes upon hospital discharge between resuscitated men and women. The nonsignificant differences between sexes may also very well be explained by an underrepresentation of female survivors. However, this does not mean that the patient-reported measures used in this study do not have clinical importance. In particular, it is well known that patients experience more symptoms than they state.[56]

Implications for Practice

As the current healthcare system does still not meet the needs of many resuscitated men and women,[1] it is worth considering if a short psychological screening instrument with integrated selected somatic symptoms used upon hospital discharge could help capture experiences of vulnerability that give rise to severe suffering and long-term emotional responses to trauma and treatment after resuscitation.[57] Most important, it seems critical to recognize early signs of fatigue and anxiety that often go unrecognized. However, it is worth noticing that emotional responses tend to be most severe in the first postarrest weeks.[7] To be alert to longer-term psychological challenges, repeated testing is warranted. Overall, a more insightful understanding of the sex-based imbalance in psychological burden on developing psychopathological manifestations using PROs is an important step toward more comprehensive assessment and person-centered care after resuscitation. In this endeavor, population-specific and robustly validated PROs are warranted.

Conclusion

In conclusion, female survivors of cardiac arrest were more likely to report worse psychological distress and illness perception and symptom burden in their immediate responses to trauma and treatment after resuscitation than male survivors of cardiac arrest. Consistent

What's New and Important

- More women than men experience difficulties in their psychological adjustment after resuscitation.
- Healthcare professionals should be aware of possible sex imbalance not only in disease trajectories after cardiac arrest but also in postarrest symptom perception at hospital discharge.
- Evaluating whether sex-stratified screening, follow-up, and rehabilitation can improve outcome should be in the focus of future cardiac arrest studies.

with sex differences in general, our results indicate that more women than men experience difficulties in psychological adjustment after resuscitation. This knowledge is useful and has important clinical implications for both nurses and survivors. By understanding the cardiac arrest survivor's perspective, nurses are better able to educate the patients on what to expect when going home. Moreover, survivors of cardiac arrest are aware of the early symptoms of distress and symptom burden, that it is normal for female survivors in particular to experience an increase in anxiety and fatigue at discharge from hospital. Overall, this may improve the current discharge practices, support the postarrest aftercare and rehabilitation, and ultimately help survivors of cardiac arrest to manage the transition to everyday life and potentially prevent long-term psychopathology.

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Paper 2a

Cognitive impairment and psychopathology in out-of-hospital cardiac arrest survivors in Denmark: The REVIVAL cohort study protocol

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BMJ Open

Cognitive impairment and psychopathology in out-of-hospital cardiac arrest survivors in Denmark: The REVIVAL cohort study protocol

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ABSTRACT

Introduction Cognitive impairment and psychopathology caused by brain hypoxia and the traumatic impact of critical illness are common in cardiac arrest survivors and can lead to negative consequences of everyday life functioning, and further impact mental health in relatives. Most studies have dealt with the mere survival rate after cardiac arrest and not with long-term consequences to mental health in cardiac arrest survivors. Importantly, we face a gap in our knowledge about suitable screening tools in the early post-arrest phase for long-term risk prediction of mental health problems. This study aims to evaluate the efficacy of a novel screening procedure to predict risk of disabling cognitive impairment and psychopathology 3 months after cardiac arrest. Furthermore, the study aims to evaluate long-term prevalence of psychopathology in relatives.

Methods and analyses In this multicentre prospective cohort study, out-of-hospital cardiac arrest survivors and their relatives will be recruited. The post-arrest screening includes the Montreal Cognitive Assessment (MoCA), the Hospital Anxiety and Depression Scale (HADS), the Impact of Event Scale-Revised (IES-R) and the Acute Stress Disorder Interview (ASDI) and is conducted during hospitalisation. In a subsample of the patients, functional MRI is done, and cortisol determination collected. At 3-month follow-up, the primary study outcomes for 200 survivors include the Danish Affective Verbal Learning Test-26 (VAMT-26), Delis-Kaplan Executive Function System tests (trail making, colour-word interference, word and design fluency), Rey's Complex Figure and Letter-number sequencing subtest of Wechsler Adult Intelligence Scale-IV, HADS and IES-R. For the relatives, they include HADS and IES-R.

Ethics and dissemination The study is approved by the local regional Research Ethics Committee (H-18046155) and the Danish Data Protection Agency (RH-2017-325, j.no.05961) and follows the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and may impact the follow-up of cardiac arrest survivors.

Strengths and limitations of this study

- A strength of the study is the prospective design and consistent follow-up with the use of standardised and validated measurement tools.
- A limitation of the study is the differential loss to follow-up, which can introduce bias and challenge the internal validity of the study.
- A strength of the study is the multicentre approach. This will improve statistical power and generalisability of the results.
- A strength of the study is its potential to contribute to a better referral from cardiac care to targeted rehabilitation services.

INTRODUCTION

The global incidence of cardiac arrest with assumed primary cardiac cause is 55/100 000 inhabitants.[1] In Europe, approximately 275 000 people with all-rhythm cardiac arrests are treated by the emergency medical systems (EMS) each year.[2] Out-of-hospital cardiac arrest (OHCA) is a significant cause of global mortality.[3] However, in recent years the survival rates have improved especially in developing countries due to advances in the chain of survival.[1] At present, the majority of published OHCA studies focus on the acute prehospital and intensive care treatment of OHCA sufferers. Far fewer studies have investigated the period from early recovery to long-term return to everyday life. The existing literature on this period highlights two critical challenges for cardiac arrest survivors in the post-arrest recovery process, first diminished neurocognitive functions and second disabling emotional difficulties.[4–7] In these survivors, long-term cognitive impairment and psychopathology constitute a major personal and family burden, as well as a public health and economic concern.[8–15] Mild to moderate cognitive sequelae are reported in up to 50% of survivors.[6 16] Transient or permanent memory loss, reduced visual–motor skills, attention deficit and executive impairment are the most dominant cognitive impairment found in this population.[5 6 17 18] Importantly, impaired cognitive functioning at 3-month post-arrest has been found to correlate with worse physical and mental health-related quality of life (HRQoL) and not being able to return to work around the first year after OHCA.[19] Cardiac-induced cerebral hypoxia cause a diffuse injury that may damage the functional integrity of the brain[20] and cause cognitive impairment.[21 22] Resting state functional MRI (fMRI) is an informative imaging method that assays functional integrity and level of communication within the brain.[23] In a recent study, patients with increased within-network and decreased between-network functional connectivity in the acute phase after cardiac arrest survival had a favourable outcome (FO) 1 year later compared with patients with a non-favourable outcome (nFO),[13] suggesting higher functional integrity in patients with an FO. This increased within-network functional connectivity was also observed in a smaller study of cardiac arrest patients with good outcome at hospital discharge.[14] To date, no reliable cognitive screening or imaging method for use during the in-patient hospitalisation that can detect risk of long-term cognitive impairment in cardiac arrest patients exists. A post-arrest screening model may contribute to prompt initiation of relevant follow-up and targeted cognitive rehabilitation.

A cardiac arrest is a severe and traumatising life event and long-term post-arrest psychopathology is prevalent.[5 24–26] Processing near-death experiences, coping with prolonged preoccupation with somatic symptoms and fear of a second cardiac arrest is a burden to many cardiac arrest patients.[5 24] Up to 61% of cardiac arrest patients experience anxiety, up to 45% depression and up to 27% post-traumatic stress disorder (PTSD).[5] In particular, anxiety and depression have been found to negatively impact HRQoL and physical health in patients up to several years after survival.[27] Furthermore, a cardiac arrest yields the highest prevalence of PTSD among cardiac disease categories,[24] and PTSD is reported to double the overall risk of mortality, recurrence of a new cardiac event and causing long-term diminished mental health and quality of life.[28 29] Little is currently known about the role of acute emotional reactions for developing long-term psychopathology in cardiac arrest survivors, but high acute stress reactions in other patient populations appear to be associated with worse long-term outcomes.[30–32] Elucidating the role of acute emotional reactions may serve to support and advice the patients about future challenges and to initiate targeted psychological interventions.

Being the close relative of a cardiac arrest survivor can cause enduring psychological strains.[33–35] Research indicates that these psychological strains are caused by a burden of witnessing the cardiac arrest, having to care for the patient and from the emotional stress of living with someone who is at risk of another cardiac arrest.[36] At 1 year post-arrest, 40% of the close relatives of patients with brain injury are still experiencing a high impact of the cardiac event and display a more severe traumatic stress level than the patient (S Armand, unpublished data, March 2020), and after 2 years these caregivers show a higher level of trauma-related stress than that observed in the general population.[37] As a growing number of patients are surviving cardiac arrest, it is crucial to focus more attention on psychological challenges in relatives in the aftermath after surviving cardiac arrest. The overall aim of the current study is therefore to evaluate and test a novel screening procedure during hospitalisation for its ability to predict at-risk patients for disabling cognitive impairment and psychopathology at 3 months. The incidence of psychopathology in close relatives 3-month post-arrest will also be explored. Overall, we expect that the screening procedure will be able to identify at-risk patients for disabling cognitive impairment and psychopathology at 3-month follow-up. In particular that:

Hypothesis 1: Lower level of cognitive impairment during hospitalisation (screening) is positively associated with cognitive outcome at 3-month follow-up.

Hypothesis 2: The strength of discrete resting-state networks in the brain assessed with fMRI during hospitalisation (screening) is positively associated with cognitive outcome at 3-month follow-up.

Hypothesis 3: Higher level of acute emotional reactions during hospitalisation (screening) is positively associated with psychopathology outcome at 3-month follow-up.

Hypothesis 4: Higher level of cognitive impairment and emotional reactions during hospitalisation in patients is positively associated with psychopathology outcomes in relatives at 3-month follow-up.

METHODS AND ANALYSIS

Study design, setting and population

The REcovery after cardiac arrest surVIVAL (REVIVAL) study is designed as a multicentre, prospective cohort study in which first-time OHCA survivors are followed for up to 1 year after the event (flowchart presented in figure 1). The study settings are three highly specialised heart centres at university hospitals in Denmark: Rigshospitalet and Herlev-Gentofte Hospital in the Capital Region of Denmark and Odense University Hospital in the Southern Region of Denmark. All cardiac arrest patients will be approached for study participation and approximately 250 in-hospital patients (≥18 years of age) with a first-time OHCA admission diagnosis will be recruited, starting 1 January 2018 and ending 31 December 2021. Only patients with a presumed cardiac cause for their cardiac arrest as defined by Utstein template will be included.[38] Both cardiac arrests as primary and secondary diagnosis will be included. Furthermore, the closest relatives will be identified and included during hospitalisation for a 3-month follow-up. Patients are excluded if they have a serious not treatable other somatic or psychiatric illness or previous cerebrovascular events or traumatic brain injury and those unable to speak and understand

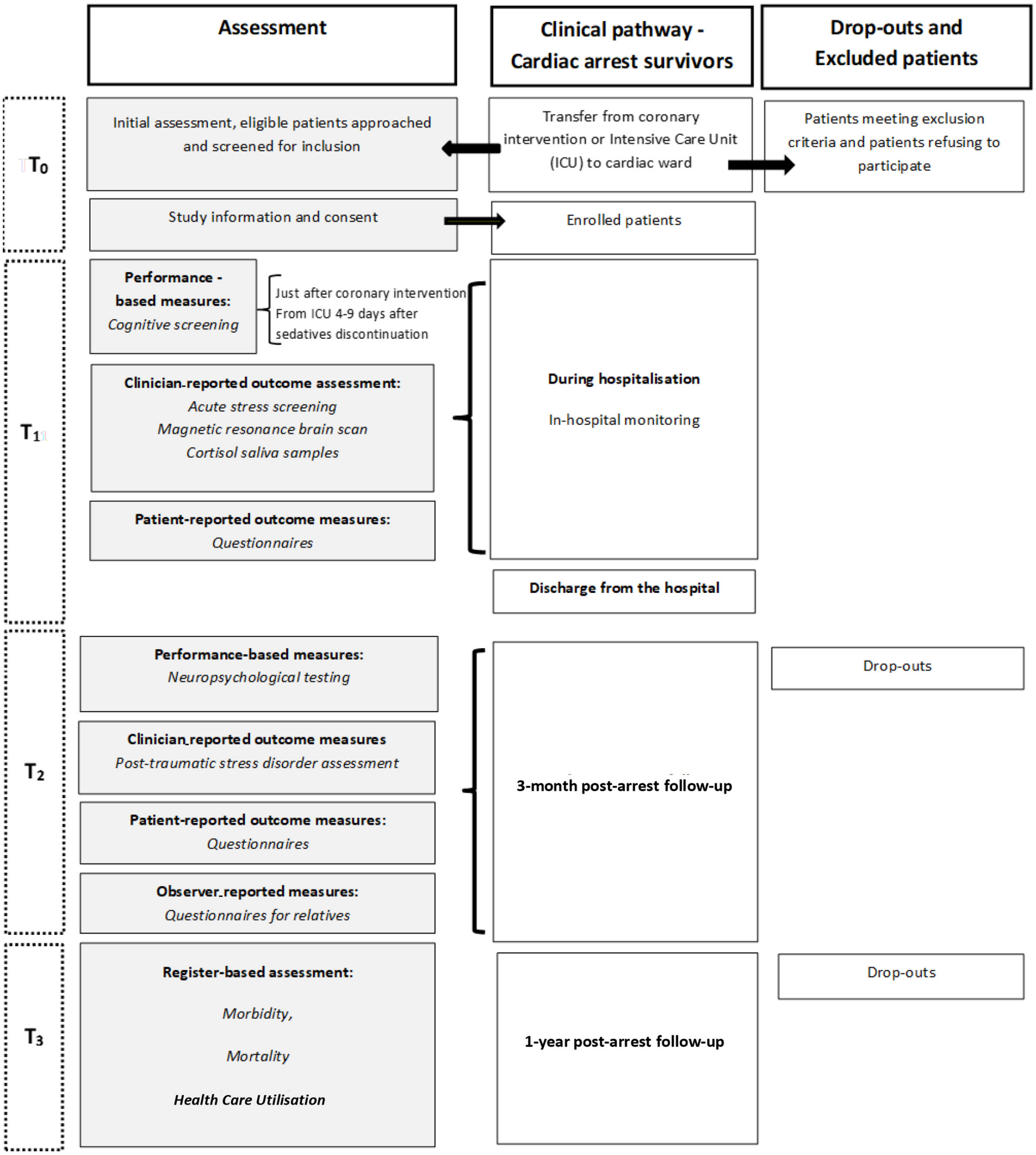

Figure 1 Flowchart of study assessment. T0: Study inclusion, T1: During hospitalisation, T2: 3-month follow-up, T3: 1-year follow-up.

Danish. The cognitive screening and neuropsychological testing require the patients to follow verbal instructions and to see the tasks presented. Therefore, patients with solid hearing or visual impairments are excluded. In a substudy exploring resting state fMRI and stress reactivity, respectively, 40 patients without contraindications to MR will be included from Rigshospitalet. The REVIVAL study is described in accordance with the current Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Guidelines for reporting observational studies).[39]

Patient selection and recruitment

All the patients and relatives are selected and recruited in the three Danish cardiology wards. OHCA survivors transferred from the intensive care units (ICUs) to the ward will be included 4 to 9 days after termination of analgosedatives to ensure no residual sedation used during therapeutic hypothermia. The survivors from the coronary care units who undergo percutaneous coronary intervention after a brief cardiac arrest without ICU admission will be included after intervention in the cardiac catheterisation laboratory (figure 1). This subgroup of cardiac arrest survivors will be included although they are awake or only had a brief period of coma after admission to the hospital and presumably recover earlier to their premorbid cognitive functioning than the critically ill patients. The patients and relatives at the included sites follow the same protocol. A trained cardiac nurse will collect most of the clinical data from the patients' charts. The same nurse will approach eligible patients during hospital admission

Table 1 The cognitive assessment

Target cognitive domain	During hospitalisation	3-month follow-up
	MoCA	Neuropsychological tests
Attention	Number sequence Letter list	D2 (visual attention) (trail making+stroop)
Visuospatial construction	Cube copying	Rey's figure
Episodic memory	Verbal memory test	VAMT-26
Working memory	Serial subtraction	Letter-number sequence
Executive functioning	Trail making B Clock drawing Abstraction	Trailmaking B D-KEFS colour-word interference
Psychomotor processing speed	Trail making B	Trail making A and B
Language	Naming Repeating Word mobilisation	
Orientation	Orientation	

D-KEFS, Delis–Kaplan Executive Function System; MoCA, Montreal Cognitive Assessment; VAMT-26, Danish Affective Verbal Learning Test-26.

on the cardiology ward and invite them to participate in the study. The patients will be assessed clinically and provided with oral as well as written information about the study. The patients are given the opportunity to read and consider the study information leaflet carefully. If the patients agree to participate, they will be asked to provide written informed consent in consultation with their closest relative prior to inclusion. This is justified in ethical issues as some patients with cognitive impairment may not feel empowered to refuse participation.

Collection of data and measures

Screening model during hospitalisation

A team of certified nurses with a background in cardiology will screen the patients. Administration and interpretation of data will take place under supervision by a trained psychologist.[40]

Cognition

The cognitive screening is conducted using the Danish version of the Montreal Cognitive Assessment tool (MoCA), V.7.0.[41] The MoCA is a brief cognitive screening test designed to identify mild cognitive impairment. The MoCA covers six cognitive domains: attention, visuospatial construction, executive functioning, memory, language and orientation (table 1) and is rated from 0 to 30. A cut-off ≥26 is considered as normal cognitive function level. In the summary score, a level of education ≤12 years is given an extra point as education level has shown to decrease the overall score.[41] The MoCA is suggested for use in the post-cardiac arrest settings,[21 42] however, it remains to be evaluated in a Danish patient population with possible hypoxic-ischaemic brain injury. The MoCA has shown high level of internal reliability with Cronbach's α=0.83 in detection of mild cognitive impairment.[41]

Mood and delirium

As symptoms of delirium often are subtle but still can have an impact on cognition, the cognitive screening is initiated with a rapid clinical assessment of delirium, using 4AT scale.[43] Furthermore, the mood state and functional independence of the patients are collected (table 2). If the study nurse is in doubt regarding patients functioning, an informed nurse or relative is asked.[44]

Resting state fMRI

Patients who meet inclusion criteria for MRI will undergo structural and functional brain imaging on a 3 Tesla Siemens Prisma MRI scanner at Rigshospitalet. Trained personnel will perform MRI scans; during transport and scanning, a trained nurse will monitor the patients. We will obtain high-resolution structural T1-weighted and T2-weighted images and T2*-weighted BOLD fMRI resting state scans (~10 min of resting state fMRI). During resting state fMRI, patients are asked to lie still with eyes closed and let their mind wander freely. Resting state fMRI data will be processed using canonical brain imaging tools, for example, SPM[45] and Conn[23] to establish region-to-region connectivity estimates while accounting for motion, physiological and other noise sources. Resting state networks will be defined based on a priori connectivity network descriptions.[46]

Psychopathology

Self-rated symptoms of depression and anxiety and trauma reactions will be collected using the Hospital Anxiety and Depression Scale (HADS-D and HADS-A)[47] and the Impact of event Scale-revised (IES-R).[48] The Hospital Anxiety and Depression Scale (HADS) is a valid and internally consistent 14-item instrument to measure anxiety and depression. Each item is scored from 0 to 3 with a summary score between 0 and 21 for either anxiety or depression. Scores of 11 and above indicate the probable presence of a mood disorder. HADS has shown a mean α of 0.83 and 0.82 for the HADS-A and HADS-D, respectively.[49] Impact of Event Scale-revised (IES-R) measures distress caused by a traumatic event is a widely used measures to assess traumatic stress symptoms with a maximum score of 88. The IES-R consist of 22 items measuring subjective distress caused by a traumatic event scored on a Likert scale from 0 (not at all) to 4 (extremely) and includes subscales for avoidance, intrusions and hyperarousal. The IES-R has shown high internal consistency with coefficient alphas ranging from 0.84 to 0.85 for avoidance, 0.87 to 0.92 for intrusion and 0.79 to 0.90 for hyperarousal.[48]

Table 2 Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors

Outcome domains and measurement instruments	Time of measure	Type of quantity
Sociodemographic variables		
Age	T0	Continuous
Sex	T0	Binary
Marital status, type of occupation, employment status, living situation	T0	Categorical
Medical variables		
Known IHD, hypertension, previous MI, PCI or CABG, chronic heart failure, diabetes mellitus, COPD and chronic kidney disease	T0	Binary
Clinical variables related to the cardiac arrest		
Place of OHCA, aetiology of cardiac arrest, initial rhythm, TTM, medication during ICU stay, LVEF	T0	Categorical
Bystander witnessed cardiac arrest, bystander performed CPR, use of AED, shockable rhythm, awake at arrival to hospital, TTM, intubated, medication during ICU, delirium at ICU	T0	Binary
Time to ROSC, intubation time, length of stay at ICU	T0	Continuous
Conscious state		
GCS	T0	Categorical
Neurological outcome		
CPC	T1	Categorical
Length of stay at hospital	T1	Continuous
Performance-based variables		
Delirium score		
4AT	T1	Categorical
Functional independence		
Barthel Index-20	T1	Categorical
Cognitive status		
MoCA	T1	Binary
Brain activity while resting		
rsfMRI	T1	Continuous
Neuropsychological outcome		
VAMT-26, D- KEFS trail-taking, D-KEFS colour-word interference, D-KEFS design fluency, Rey's complex figure and Letter-number sequencing: subtest of WAIS-IV	T2	Binary
Cortisol awakening response	T1	Continuous
Patient-reported outcome measures		
POMS	T1	
HADS, IES-R, CSS	T1, T2	Continuous
B-IPQ, FSS, HeartQoL, SF-12, PSQI, CISS, BRIEF-A, ECR-R, AMCQ, CES-S, MTEQ, PTGQ, ACQ, NDEQ	T2	Continuous
Lifestyle changes, health profile	T2	Categorical
Register based		
Depression, anxiety, dementia, chronical fatigue syndrome and heart failure, mortality and healthcare utilisation	T3	Continuous

ACQ, Attribution; AED, automated external defibrillator; AMCQ, Autobiographical Memory Characteristics Questionnaire; B-IPQ, Brief Illness Perception Scale; BRIEF-A, Behavior Rating Inventory of Executive Functions, adult version; CABG, coronary artery bypass surgery; CES-S, Centrality of Events–Short; CISS, Coping Inventory for Stressful Situations; COPD, chronic obstructive pulmonary disease; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; CSS, Crisis Support Scale; D- KEFS, Delis–Kaplan Executive Function System; ECR-R, Experience in Close Relationships; FSS, Fatigue Severity Scale; GCS, Glasgow Coma Scale; HADS, Hospital Anxiety and Depression Scale; ICU, intensive care unit; IES-R, Impact of Event Scale-Revised; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MoCA, Montreal Cognitive Assessment; MTEQ, Memory of Event Scale; NDEQ, Near-death Experience Questionnaire; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Inventory; PTGQ, Post-Traumatic Growth Questionnaire; ROSC, return of spontaneous circulation; rsfMRI, resting state functional magnetic resonance imaging; SF-12, 12-item Short Form Survey; T0, pre-arrest, medical and clinical data; T1, during hospitalisation; T2, 3 months follow-up; T3, 1 year follow-up; TTM, targeted temperature management; VAMT-26, Danish Affective Verbal Learning Test-26.

Acute stress disorder

The Acute Stress Disorder Structured Interview (ASDI) is a 19-item clinical interview, which investigates the incidence and severity of acute stress responses operated as acute stress disorder (ASD) in DSM-5 in the month following trauma exposure.[50 51] ASD is divided into five symptom clusters: intrusive memories or revival, negative mood, dissociation, avoidance and arousal. To meet the criteria for ASD, the patient must have experienced a traumatic event (in this case a cardiac arrest) during the past month (criteria A) as well as the presence or deterioration of at least nine symptoms independent of the associated category after the onset of episode (Criterion B), which should occur within 3 days to 1 month (Criterion C).[52]

Cortisol awakening response

At the same day as the structured clinical interview (ie, ASDI) is performed, saliva samples for determination of the cortisol awakening response (CAR) will be obtained from eligible patients. Five samples are collected during awakening and three saliva samples will also be collected during the day at 12, at 18 and at 23 o'clock. The total amount of saliva per patient is 16 mL. After collecting the saliva, the samples will be stored and analysed at the Department of Clinical Biochemistry, Rigshospitalet, Glostrup.

Sociodemographic variables and several clinical prehospital and inhospital data were obtained from electronic medical records (see table 2).

At 3-month follow-up

The patients included at Rigshospitalet and Herlev-Gentofte Hospital will undergo a detailed and individual neuropsychological assessment at the Neurobiology Research Unit at Rigshospitalet, and patients included at Odense University Hospital will be assessed with a similar test battery at the University of Southern Denmark. The cognitive assessment of the patient's cognitive functions will be given, administered and interpreted by a clinical and trained psychologist or psychology student under supervision. The patients and their relatives will furthermore complete a package of self-reported questionnaires.

The neuropsychological assessment

The tests used are a carefully selected neuropsychological test battery comprising some of the same subcomponents as for the MoCA; attention, visuospatial construction, executive functioning, episodicmemory, working memory and psychomotor processing speed. The tests used are all validated in clinical settings for a variety of populations and have shown good test–retest reliability. To address a source of bias, all tests are conducted by a psychologist, who is kept blind of the clinical data as well as the results of the previous brief cognitive screening. A detailed outline of the neuropsychological tasks includes Danish Affective Verbal Learning Test-26 (VAMT-26)[53] and Delis-Kaplan Executive Function System tests (D-KEFS) comprising trail making, colour-word interference, design fluency and word fluency[54] together with the Rey's complex figure test[55] and Letter-number sequencing test from the Wechsler Adult Intelligence Scale-IV (WAIS-IV)[56] (table 1).

Psychopathology in patients

Furthermore, the patients will repeat the self-reported questionnaires identical to the questionnaires completed during hospitalisation: HADS-D, HADS-A and IES-R.

Psychopathology in relatives

The relatives are also asked to complete the HADS-D, HADS-A and IES-R. The questionnaires for both patients and their relatives are sent via e-mail 2 weeks before the 3 months follow-up.

At 1-year follow-up

The 1-year follow-up is designed as register-based (table 2). To investigate whether baseline data are associated with morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure and with mortality and healthcare utilisation, the collected data will be linked with data from national administrative registers; the Danish National Patient Register,[57] the Danish Civil Registration System,[58] the Danish National Prescription Registry,[59] the Danish education registers[60] and the Danish registers on personal income and transfer payments.[61]

Primary and secondary study outcome measures

Primary outcome measures for patients

The primary outcome is whether the patients present an FO or an nFO at 3-month follow-up. To elucidate cognition and psychopathology separately, primary outcomes will be established for each of these domains.

Cognition

As primary cognitive outcome, the patients will be divided into two groups, FO and nFO, based on their performance in the neuropsychological tasks. The subset with an nFO is defined as minimum 1.5 SD under the norm or reference data[53–55 62] on minimum one test or 1 SD on two or more tests. The rest of the patients fall into the FO group.

Psychopathology

As primary psychopathology outcome, the patients will be divided into two groups, FO and nFO, based on their scores on the HADS and IES-R. The subset with an nFO is defined one or more scores above cut-off for psychopathology on the HADS and IES-R: HADS-D and HADS-A >8 and IES-R >24. The rest of the patients fall into the FO group.

Secondary outcome measures for patients

Secondary outcomes for patients are self-reported measures of sleep quality, fatigue, executive functioning and HRQoL at 3 months of follow-up (table 2). A detailed

Table 3 Outcome domains, measurement instruments and measurement time for the relatives

Outcome domain	Measurement instruments	Time
Demographic variables and psychiatric medical history		T2
Health-related quality of life	SF-12	
Anxiety and depression	HADS	
Distress caused by a traumatic event	IES-R	
Experience in close relationships	ECR-R	
Social support after a crisis	CSS	
Major depression	MDI	
The extent to which an event is viewed as being central to one's identity	CES-S	
Cognitive decline reported by informants (relatives or close friends)	IQ-CODE	

CES-S, Centrality of Event short; CSS, The Crisis Support Scale; ECR-R, Experience in Close Relationships; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Event Scale-Revised; IQ-CODE, The Informant Questionnaire on Cognitive Decline in the Elderly; MDI, Major Depression Inventory; SF-12, 12-item Short Form Survey; T2, 3-month follow-up.

description of the secondary outcomes is described in the online supplemental material 1. Secondary outcomes for patients also include register-based information of morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure, mortality and healthcare utilisation at 1-year post-arrest (table 2).

Primary outcome measures for relatives

The primary outcomes for the relatives include HADS-D, HADS-A and IES-R[47 63] (table 3).

Secondary outcome measures for relatives

Secondary outcome measures for relatives include self-reported HRQoL, experience of cognitive changes in the patient after the cardiac arrest, social support, major depression, the quality in the relationship with the cardiac arrest survivor and the extent to which the cardiac arrest is viewed as being central to one's identity (table 3).

Several exploratory outcomes will also be collected (figure 1).

Data analysis plan

The collected sociodemographic data will be presented as means±SD or percentages, respectively, and group differences will be calculated by t-tests (continuous data) or χ^2 (categorical data). Appropriate regression models will be used to examine the associations between screening performance during hospitalisation and the primary and secondary study outcomes. In all model's relevant covariates, for example, sex, age, comorbidity, time to return of spontaneous circulation, coma duration time, time at ICU, time of hospitalisation will be included (table 2). A formal power calculation of sample size has not been performed due to the several aims and potential analyses of this study. With no comparative patient groups and only few small existing studies, we aim for a sample size of 200 cardiac arrest survivors at 3-month follow-up for the primary outcome to be statistically and clinically significant.

Patient and public involvement

As a patient involvement method, two theme-based sessions involving direct patient feedback have been carried out in the early pilot and design phase of the study. The aim of these sessions was to (1) identify patient preferences regarding the cognitive screening procedure (figure 2) and (2) develop the research priorities including implementation of possible changes based on the patient's feedback. Data derived from the theme-based patient feedback sessions provides the basis for the cognitive screening procedure in the REVIVAL study. To ensure further patient involvement, we plan to engage the patients in the planning phase of disseminating the results.

DISCUSSION

To the best of our knowledge, the present study will be the largest study evaluating and testing a novel screening procedure for cognitive impairment and emotional reactions during hospitalisation in a population of OHCA survivors. As the incidence of cardiac arrest survival is increasing, establishing a standardised approach to screening in OHCA survivors will be critical in the future. Following the aims of the study and to strengthen the standardisation of the results, only patients with a presumed cardiac cause for their cardiac arrest as defined by Utstein template will be included. Since a common single aetiology of cardiac arrest is respiratory failure, it could be

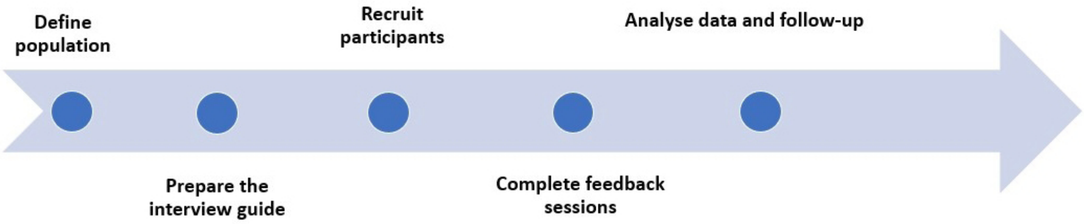

Figure 2 Direct patient feedback.

considered to include this population in a future study. Although cognitive and mental health outcomes in OHCA survivors may be comparable with other medical populations,[7 64 65] the study does not contain a comparative arm as it does not aim to investigate a specific intervention. Instead, the study seeks to investigate OHCA survivors after standard treatment in a naturalistic setting. Due to the nature of the study and the vulnerable state of the patients, differential loss to follow-up is expected in the study. To elucidate data missing not at random, we plan to conduct phone calls to non-responders at 3-month follow-up regarding their withdrawal from the study. We expect that results from the REVIVAL study will inform an early screening procedure of OHCA survivors in clinical settings as well as inform future targeted rehabilitation in survivors who are likely to develop protracted cognitive impairment and psychopathology.

Ethics and dissemination

There is little to no discomfort for the patients and their relatives in this study. Due to the weakened constitution of the patients, the neuropsychological test at 3-month post-arrest could be experienced as taxing and can be divided into 2 days. The study complies with the Declaration of Helsinki and has been approved by the Danish National Committee on health research ethics (H-18046155) and the Danish Data Protection Agency (RH-2017-325, I-Suite no: 05961). Patients and their relatives will receive oral and written information about the study and inclusion will require obtained written consent for all participants before enrolment. Results from this study will be disseminated at regional, national and international conferences and in peer-reviewed journals.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

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Paper 2b

Cognitive impairment and psychopathology in sudden out-of-hospital cardiac arrest survivors: Results from the REVIVAL cohort study

Manuscript in final preparation

Cognitive impairment and psychopathology in sudden out-of-hospital cardiac arrest survivors: Results from the REVIVAL cohort study

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Abstract

Aim

To investigate cognitive impairment and symptoms of psychopathology in out-of-hospital cardiac arrest survivors using a novel screening procedure during hospitalisation, and to examine the evolution of these parameters at three-month follow-up.

Methods

This was a prospective multicenter cohort study. During hospitalisation we screened for cognitive impairment using the Montreal Cognitive Assessment, and for symptoms of anxiety, depression and traumatic distress using the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale–revised (IES-R). At follow-up, cognitive impairment was evaluated with a selected neuropsychological test battery and psychopathology with repeated HADS, and IES-R. Logistic regression models were applied to test associations between screening results and outcomes.

Results

A total of 297 cardiac arrest survivors were included. Overall, 65% presented with early cognitive impairment and 53% at follow-up. Early cognitive impairment and a non-favorable cognitive outcome were associated (odds ratio [OR]: 2.54; 95% confidence interval [CI]: 1.43-4.51). A total of 25% reported early symptoms of anxiety, and 17% had clinical levels of anxiety at follow-up, 20% reported early symptoms of depression, and 15% had clinical levels of depression at follow-up, 21% reported early symptoms of traumatic distress, while 19% had clinical levels of post-traumatic stress disorder (PTSD) at follow-up. Early symptoms of anxiety and clinical levels of anxiety (OR: 6.70; 2.40-18.72), early symptoms of depression and clinical levels of depression (OR: 4.69; 1.69-13.02) and early symptoms of traumatic distress and clinical levels of PTSD (OR: 7.07; 2.67-18.73) were associated.

Conclusion

Most survivors exhibited cognitive impairment and symptoms of psychopathology during hospitalisation, which were associated with non-favorable mental health outcomes at three months.

Key terms: Resuscitation, Montreal Cognitive Assessment, Mild cognitive impairment, Psychopathology, Screening tool

Introduction

While sudden out-of-hospital cardiac arrest (OHCA) is still a leading cause of death worldwide,[1] survival rates are higher than ever before due to successful improvements in prehospital and acute medical care regimes.[2,3] In Europe and the United States of America, the survival rates at hospital discharge are, on average, 8% and 11%, respectively.[4] In many cases, however, mental health complications are a pervasive secondary consequence of resuscitation,[5-8] and cognitive impairment and symptoms of psychopathology are common.[5,8,9] Roughly 50% of cardiac arrest survivors report long-term cognitive impairment,[9] and prolonged psychopathological symptoms of anxiety (15-24%), depression (13-15%), and post-traumatic stress disorder (PTSD) (16-28%) are prevalent.[7,8] These are mental health challenges that deeply affect the survivors recovery,[10,11] interfere with their health-related quality of life,[12-14] and predict lower post-resuscitation participation in society.[15]

Current European Resuscitation Council (ERC) and European Society for Intensive Care Medicine (ESICM) guidelines for post-resuscitation care recommend systematic functional assessments before hospital discharge,[16] however, screening for possible cognitive and psychological problems is still not routine in cardiology. Furthermore, no screening tool has been developed for the detection of cognitive impairment and symptoms of psychopathology, specifically for OHCA survivors, so these challenges often go unrecognised.[17] The ERC and ESICM advocate assessing cognitive impairment systematically with the performance-based Montreal Cognitive Assessment (MoCA) tool, and symptoms of anxiety and depression with the self-reported questionnaire Hospital Anxiety and Depression Scale (HADS-A and HADS-D), respectively.[16] Furthermore, the self-reported questionnaire Impact of Event Scale (IES) has been suggested as a screening tool for measuring traumatic distress, including PTSD.[17] However, more knowledge is needed about the usefulness of these cognitive and psychological screening tools of OHCA survivors during hospitalisation.

To fill this knowledge gap, this prospective multicenter cohort study was designed to investigate cognitive impairment and symptoms of psychopathology in OHCA survivors using a novel screening procedure during hospitalisation, and to examine the evolution of these parameters at three-month follow-up. We hypothesised that cognitive impairment during hospitalisation would be associated with a cognitive non-favorable outcome (nFO) at three-month follow-up, and that symptoms of psychopathology during hospitalisation would be associated with clinical levels of psychopathology at three-month follow-up.

Methods

Study design and recruitment procedures

The multicenter REcovery after cardiac arrest surVIVAL (REVIVAL) cohort study (*n*=297 patients) was conducted at three highly specialised Heart Centre in Denmark between December 2017 and February 2022. According to international guidelines, the cardiac arrest centres in Denmark have protocols for the treatment and care of resuscitated patients, including interventional cardiology, bundled critical care with targeted temperature management, protocolised cardiorespiratory support and prognostication.[16] The protocol for the current study has been previously published.[18]

In- and exclusion criteria

Inclusion criteria were unconscious or conscious first-time OHCA survivors with sustained return of spontaneous circulation (ROSC) and with a suspected cardiac aetiology for their cardiac arrest as defined by the Utstein template.[19] Exclusion criteria were patients who had a history of cerebrovascular or traumatic brain injury, were suffering from a serious untreatable somatic or psychiatric disease or lacked Danish language abilities to complete the screening procedure.

Recruitment

Comatose patients were approached preferably on day four (≥72 hours) after the sedatives were terminated. Patients admitted awake were approached for participation when clinically stable. All patients gave their informed written consent after consulting with a close relative.

Ethics

The REVIVAL study complies with the ethical principles as described by the Declaration of Helsinki.[20] The Danish Data Protection Agency approved the handling of data journal no: RH-2017-325, I-Suite no: 05961, and the regional Research Ethic Committee (H-18046155) approved the study before inclusion of patients.

Data collection and measures

Data collected during hospitalisation (T1)

Data collected during hospitalisation (T1 data) included socio-demographic data, medical pre-arrest history, clinical characteristics related to cardiac arrest, MoCA, HADS and IES-R. The screening was conducted by a certified cardiac project nurse in a quiet setting during hospitalisation at Copenhagen University Hospital, Rigshospitalet, at University Hospital Herlev-Gentofte, and at Odense University Hospital. For the patients admitted awake after a brief time to ROSC, the median time for T1 data collection was 4 days (interquartile range [IQR]: 1-5). For the patients admitted comatose, the median data collection time was 6 days (IQR: 5-8) after termination of sedatives. The most common reason for early assessment (<4 days) of the comatose patients was impending transfer to another hospital, whereas the most common reasons for overall delayed assessment (>9 days) were psychological distress and mental exhaustion.

Data collected at three-month follow-up (T2)

Data collected at three-month follow-up (T2 data) included test performances on a neuropsychological test battery, and repeated HADS and IES-R that were sent to the participants per email and completed online. Trained psychology students or a cardiac nurse administered the neuropsychological test battery following a predefined written study manual. The assessment took place in undisturbed test-facilities at the hospital. Due to the COVID-19 pandemic situation, we allowed for the neuropsychological testing to take place in the homes of a few of the patients (n=21), and six patients had a delayed follow-up assessment. The overall median time from T1 to T2 data collection was three months (IQR: 3-3.5).

Measures

Socio-demographic, medical history, and clinical characteristics

At T1, we collected self-reported socio-demographic variables comprising age, sex, ethnicity, cohabitation, level of education and occupational status prior to the cardiac arrest. To graduate highest levels of education, the International Standard Classification of Education (ISCED)[21] was adopted and divided into three groups (**Table 1**). Medical pre-arrest history variables and clinical characteristics related to the cardiac arrest, were retrieved from pre-hospital records and medical charts from all sites.

Montreal Cognitive Assessment

At T1, we screened the survivors´cognitive status using the Danish version 7.0 of the brief cognitive paper and pencil screening tool Montreal Cognitive Assessment (MoCA).[22] The MoCA is a global screening tool recognised as the preferred screening instrument for assessing post-arrest cognitive impairment.[4] Administration of the MoCA takes approximately 10 minutes and is divided into tasks covering the general domains of cognition: visuospatial abilities and executive functioning, memory, attention, language, and orientation. The instrument contains 30 items (each scored with 1 point) where a higher score reflects better performance. In addition to the scores of each item, 1 point is added for education level <12 years. In this study, we used the suggested threshold ≥26 indicating a normal cognitive functional level. Those with scores <26 were thus suspected of cognitive impairment.[22,23]

The neuropsychological test battery

At T2, all participants underwent an extensive neuropsychological test battery to assess performance in the following three main cognitive domains: episodic memory, visuospatial abilities, and executive functioning (**See Supplementary Material S1**). The test battery comprised: The Verbal Affective Memory Task-26,[24] Rey's Complex Figure,[25] Delis-Kaplan Executive System tests,[26] including Trail making Test, Verbal fluency Test, Design Fluency Test and Colour-word-interference Test. In addition, the Letter-number sequencing Test from the Wechsler Adult Intelligence Scale-IV[27] was administered. As our primary cognitive outcome, test performances were dichotomised into whether the patients exhibited a favorable outcome (FO) or nFO, the latter defined as 1.5 SD on 1 test or 1 SD on ≥2 tests below the norm population mean or reference data mean. The reference data was stratified according to age and means were calculated for each age group for comparisons with patient data**.**

Psychopathological screening

At T1 and T2, we evaluated symptoms of anxiety, depression and traumatic distress using the Danish patient-reported outcome versions of the 14-item HADS and the 22-item IES-R. The HADS scale[28] comprises two subscales (HADS-A=anxiety and HADS-D=depression) with seven items for each subscale, and evaluates the past seven days. Items are rated on a 4-point Likert scale ranging from 0 (“no symptoms”) to 3 (“extreme symptoms”). The IES-R evaluates the last seven days. Items are rated on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("extremely"). Using the total scores, we employed a cut-off score of ≥8 on HADS for the likely presence of anxiety and/or depression[29] and a cut-off score of ≥30 on IES-R for a likely presence of traumatic distress.[30]

Data analyses

We presented summary statistics of socio-demographical, medical history and clinical data related to the cardiac arrest as proportions with percentages (%) for categorical variables, means with standard deviations (M±SD) for continuous approximately normally distributed data, and medians with interquartile ranges (IQR) for non-normally distributed data. The descriptive distribution of MoCA subscale scores was illustrated with box-and-whisker plots. We compared socio-demographic data, medical histories, and clinical characteristics of non-responders of HADS and IES-R during hospitalisation and dropouts at the follow-up to the participants using persons X^2 and Fishers Exact tests. Moreover, MoCA, HADS and IES-R scores during hospitalisation for those survivors we lost contact to at follow-up were compared to the participants at follow-up using Wilcoxon rank-sum tests. Differences between patients admitted unconscious and conscious on cognitive and psychopathological measures during hospitalisation and at three-month follow-up were compared using Student’s *t*-tests and Chi-square tests.

Neuropsychological data at follow-up were transformed into z-scores, using means and standard deviations from norm or reference data. Accordingly, the patients were divided into FO and nFO groups. Effect of sex,[22,31,32] age,[22] conscious state upon admission[6] and time to ROSC,[33] applying Persons $\chi 2$ tests, Student *t*-tests and Wilcoxon rank sum-tests as appropriate.

Four multiple logistic regression models were used to examine associations between MoCA, HADS-A, HADS-D and IES-R during hospitalisation and follow-up outcome measures of neuropsychological status (FO and nFO) and clinical levels of psychopathology. In all regression models age, sex, conscious state of admission and time to ROSC were included as covariates. Estimates are presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). P-values were adjusted using Holm–Bonferroni for four tests. Data were analysed using STATA 15.1 (StataCorp, 2017; Stata Statistical Software: Release 15, Stata Corp LLC, College Station, Texas). Data description was reported according to the STROBE guidelines related to observational study reporting.[34]

Results

T1 participant characteristics

Socio-demographic, medical history, and clinical characteristics

A total number of 665 OHCA survivors were identified as admitted and treated at the participating cardiac arrest centres (**Figure 1**). Due to exclusion and deaths, a total of 297 OHCA survivors (16% women) were encrolled. Of these,188 patients were hospitalised unconscious. Baseline socio-demographic, medical history and clinical characteristics are presented in **Table 1.** The ethnic majority group (98%) was Caucasian with Danish descent. The remaining 2% had Asian or Middle Eastern descent, but all with good Danish proficiencies. Median age of the included survivors was 59 years (IQR: 50-67). Female survivors were younger 54 years (IQR: 44-61) than the male survivors 60 years (IQR:, 51-68), p=.001).

MoCA scores during hospitalisation

As depicted in **Figure 1**, all 297 survivors were screened with MoCA. The total MoCA median score was 24 (IQR: 21-26), with 65% exhibiting cognitive impairment as indicated by a MoCA score <26. The most predominant cognitive domain affected was impaired memory, followed by problems with visuospatial abilities and executive functioning (**Figure 2**). On the whole, the MoCA language domain escaped impairment. Survivors with a MoCA score <26 were older than the MoCA ≥26 group (60 years (IQR: 61-69) vs. 57 years (IQR: 48-54), p=.001), and were more often admitted unconscious at the ICU (72% vs. 52%, p=.001) **(Table 2)**. There were no significant effects of sex and time to ROSC.

HADS and IES-R scores during hospitalisation

As presented in **Figure 1**, 269 survivors completed the HADS and 264 completed the IES-R. The median HADS-A score was 5 (IQR: 2-8), and 25% reported symptoms of anxiety (HADS-A score ≥8). Survivors with a HADS-A ≥8 were more often admitted unconscious at the ICU (29% vs. 18%, p=.02) compared to survivors with a HADS-A score <8 **(Table 2).** The median HADS-D score was 3 (IQR: 1-7), and 20% reported symptoms of depression (HADS-D score ≥8). Moreover, the median IES-R score was 17 (IQR: 8-27), with 21% reporting symptoms of traumatic distress as indicated by an IES-R score ≥30. Survivors with an IES-R score ≥30 were younger compared to survivors with an IES-R <30 (58 years (IQR: 47-64) vs. 60 years (IQR: 51-68), p=.04) and had a longer time to ROSC (15 minutes (IQR: 10-20) vs. 10 (IQR: 7-15), p=.005).

Non-responders of HADS and IES-R

The small group who were non-responders during hospitalisation (T1 HADS: n=28 and IES-R: n=33) did not differ from participants according to socio-demographic, medical history, and clinical characteristics**.**

T2 outcomes

T2 participants characteristics at follow-up

At T2, 294 of the overall population were alive. Of these, 28% were lost to follow-up, leaving a total number of 202 who underwent neuropsychological testing. These participants had a higher level of education (ISCED 3-8) (84% vs. 80%, p=.01), and less exhibited a MoCA score <26 (median 25 vs. 24, p<.001) compared to the overall population. Overall, 48% of the T1 responders of HADS and IES-R and 65% of the neuropsychological tested completed the questionnaires, respectively.

Non-favorable cognitive outcome at follow-up

A depicted in Table 2, a total of 107 patients (53%) exhibited a cognitive nFO. All cognitive domains were affected. Comparing patients in coma at admission with survivors admitted awake, a negative effect of coma on a cognitive nFO was observed (54% vs. 52%, p=.04) **(Table 2)**. No significant effects of age, sex, or time to ROSC were found.

Clinical levels of psychopathology at follow-up

A total of 129 survivors completed the HADS and IES-R at T2 **(Table 2),** with median HADS-A score of 3 (IQR: 1-5), and 17% reporting clinical levels of anxiety. The median HADS-D score was 2 (IQR:

0-5) with 15% reporting clinical levels of depression. Moreover, the median IES-R was 10 (IQR: 6-21) with 19% reporting clinical levels of PTSD. Compared to male survivors, female survivors were more often found with clinical levels of anxiety (46% vs. 10%, p<.001) and PTSD (54% vs. 9%, p<.001). No significant between group differences in age, conscious state at admission or time to ROSC were found.

Associations between MoCA during hospitalisation and cognitive outcome at follow-up

The unadjusted logistic regression model showed statistically significant increased odds of exhibiting a cognitive nFO at T2 with a MoCA score <26 at T1 (OR: 2.54; 95% CI: 1.43-4.51). A significant association with age was observed in the adjusted model (p= .001), while no association with sex was observed.

Association between HADS and IES-R during hospitalisation and at follow-up

Symptoms of anxiety at T1 was statistically associated with clinical levels of anxiety at T2 (OR: 6.70; 2.40-18.72) and symptoms of depression of T1 associated with clinical levels of depression at T2 (OR: 4.69; 1.69-13.02). Using IES-R as an early screener at T1, we also found a strong significant association with clinical levels of PTSD at T2 (OR 7.07: 2.67-18.73). Female sex was a strong predictor of clinical levels of anxiety (HADS ≥8) and PTSD (IES≥30) at T2. In particular, symptoms of traumatic distress at T1 was associated with clinical levels of PTSD (p<.001) in female survivors at T2. No effect of age was found.

Discussion

This multicentre prospective cohort study extends previous research on cognitive impairment and psychopathology in OHCA survivors as we found a novel screening procedure consisting of MoCA, HADS and IES-R during hospitalisation associated with mental health outcomes at three-month follow-up in a large cohort of solely OHCA survivors.

MoCA as an early marker of cognitive impairment at follow-up

Using the total standard MoCA threshold of 26, the survivors were found with difficulties with memory, visuospatial abilities and executive function which conform with previous research.[5,9] We only found minor deficits in attention tasks, which might be explained by a lack of sensitivity in the MoCA tool causing ceiling effects. Instead, we found challenges in the visuospatial tasks, which could possibly indicate that these tasks, as highlighted by Blennow et al. may be connected to executive dysfunction rather than being independent cognitive issues.[10] As expected, we note that the percentage of in-hospital survivors who were cognitively impaired was significantly higher in the two-thirds of patients admitted unconscious compared to the awake survivors. These findings are in keeping with the multidimensional concept of post-intensive care syndrome (PICS), which encompasses neuropsychiatric disabilities in the aftermath of critical illness.[35]

The prevalence of cognitive impairment found at follow-up further aligns with previous studies.[5,9] Although several studies report long-term cognitive impairment after cardiac arrest only small existing cardiac arrest studies have, to our knowledge, applied the MoCA in a screening procedure before home coming.[36,37] Therefore, we add important information to the existing research with the association between the selected MoCA threshold and cognitive nFO at three-month. First, this finding complements a cohort study[38] which found early cognitive screening with the MoCA threshold <26 as a good marker of long-term cognitive impairment in a stroke population. Second, ERC and ESICM[16] recommend the MoCA tool as an easy-to-use screening tool, and third, it correlates well with comprehensive neuropsychological tests.[39] Therefore, to identify at-risk survivors of cognitive impairment and to support their recovery, the MoCA might have the potential to be used as a screening tool in in-hospital settings.

HADS and IES-R as early markers of clinical levels of psychopathology at follow-up

Using the HADS with a threshold of ≥8, the prevalence of in-hospital survivors reporting probable symptoms of anxiety and depression is in line with previous research.[32] Thus, compared across cardiac diagnoses in the Danish nationwide DenHeart study,[40] the levels of anxiety and depression in patients with heart failure were noticeably poorer than this cohort. Also, it is worth noticing that one-third of this cohort were non-ICU responders. Therefore, one could argue that our study did not collect HADS in the most critically ill survivors with a higher prevalence of co-morbidity as heart failure. Hence, the proportion of survivors reporting symptoms of anxiety and depression might be higher. As a suggested, post-arrest screening tool for traumatic distress and PTSD is warranted, our findings using the IES-R, with a threshold of ≥30 during hospitalisation, are in line with existing research. In a consecutive sample of in- and OHCA survivors Agarwal and colleagues found approximately one-third reporting cardiac-induced PTSD symptoms before discharge.[41] In addition, a large US report supports that high levels of psychopathology are most prevalent in younger survivors.[42] Additionally, the clinical levels of psychopathology found at follow-up, are quite similar to findings reflected in the body of evidence.[7,8,43-47] Using HADS and IES-R as early markers of clinical levels of psychopathology at follow-up, we found strong associations. To our knowledge, it has not been previously suggested to include the IES-R as an early screener in cardiac arrest survivors. Still, we suggest using both the HADS and IES-R to identify the most vulnerable survivors in need of support, referring them for a trained professional if needed. In corroboration with existing findings, we noted that female sex was a strong predictor of clinical levels of psychopathology at follow-up.[42]

Limitations

The main limitation of our study design is its observational nature, which does not allow us to draw any conclusions on causal relationships. To investigate the effect of the cardiac arrest on cognitive impairment and clinical levels of psychopathology, we included strict exclusion criteria. We recognise the risk of bias from not including a control group, and not knowing the pre-arrest cognitive and psychological status of participants. Hence, those bias may impact the external validity of the study findings. Future research should account for estimates of the cognitive reserve by categorising survivors based on their reading abilities as a proxy for premorbid function.[46,48]

As expected the most critical ill survivors were lost to follow-up. As we were unable to collect cognitive and psychopathological data in the survivors we lost contact to, missing data at follow-up might have challenged the internal validity of the study and influenced our main conclusions. Although findings from our cohort add valuable knowledge to the establishing of a standardised early mental health screening approach to OHCA survivors, this is of particular importance as the follow-up survivors differed in levels of education and cognitive function during hospitalisation when compared to the overall population.

Conclusions

The REVIVAL study found cognitive impairment and symptoms of psychopathology common during hospitalisation. The hypotheses regarding associations between cognitive impairment during hospitalisation and a cognitive nFO at three-month follow-up, and symptoms of psychopathology during hospitalisation and clinical levels of psychopathology at three-month follow-up were supported. Emphasising the importance of early routine screening OHCA survivors during hospitalisation. MoCA, HADS and IES-R seem to have potential to be used as screening tools in future intervention trials, that are desperately needed.

Declaration of conflicting interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. Due to the General Data Protection Regulation, the data that support the findings of this study are not readily available. Data in the Cimbi database can be accessed by application (www.cimbi.dk/db).

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Statement of Authorship

Study design (MKW, SKB, CH, DSS)

Collection of data inluding neuropsychological testing (MKW, DSS).

Statistical analysis (MKW, OE, DSS)

Manuscript writing and submission of the manuscript (MKW, SKB, CH, BB, TBR, OE, DSS)

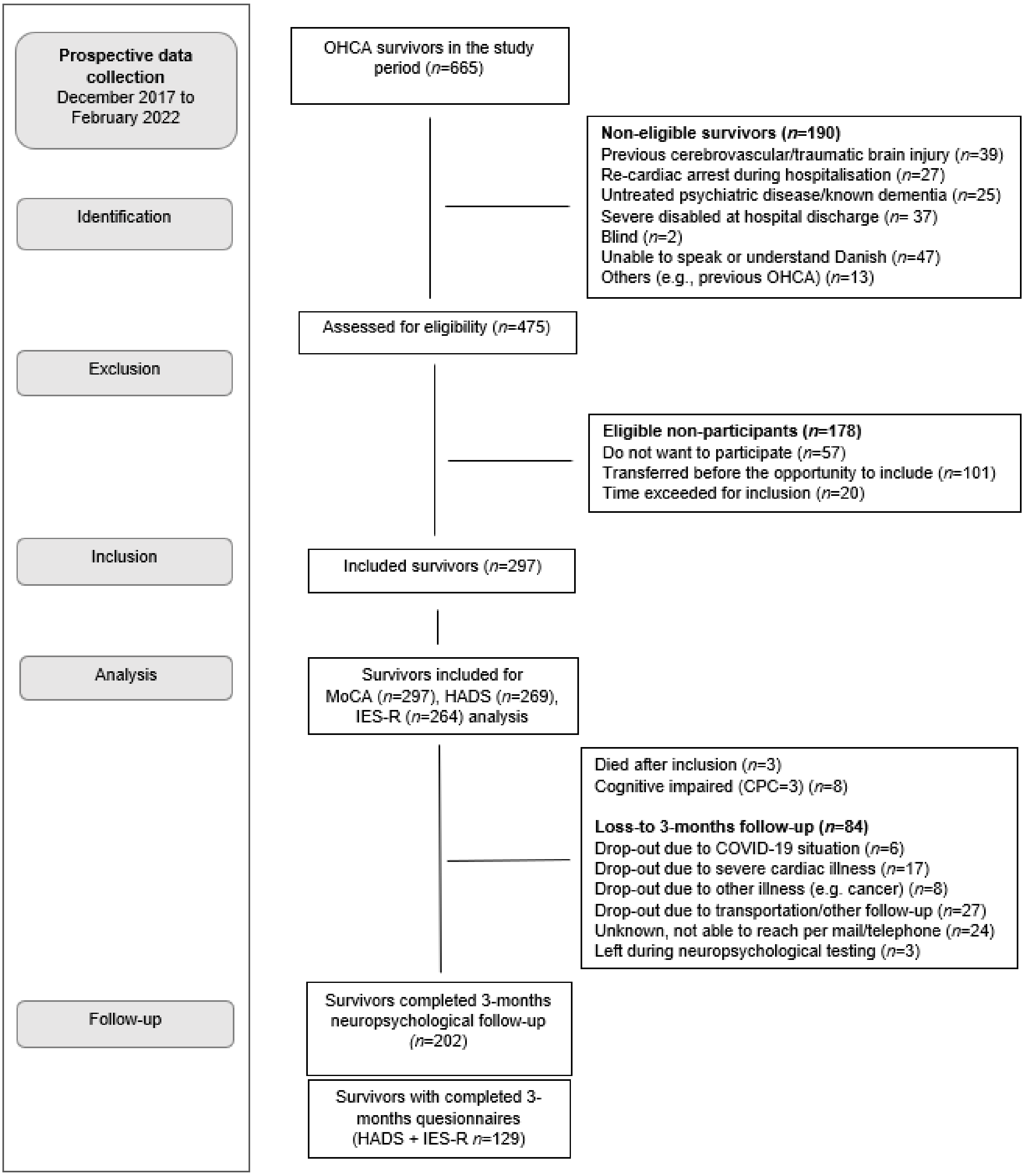

Figure 1. The REVIVAL Flow chart is in line with the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) statement (www.strobestatement.org).

OHCA: Out-of-hospital cardiac arrest, **MoCA**: Montreal Cognitive Assessment, **HADS:** Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event Scale – revised

Table 1: Baseline patient and cardiac arrest characteristics

Patient characteristics	**Total population** ***n* = 297**
Age, mean (SD), years median (IQR), years	58.2 (12.7) 59 (50-67)
Male sex, %	84
Married/ living with partner, %	82
Level of education	
ISCED levels 0-2, %	20
ISCED levels 3 and 5, %	60
ISCED levels 6-8, %	20
Occupational status prior to cardiac arrest	
Working full- or part-time, %	60
Not working (e.g., retired or on sick leave), %	40
Medical pre-arrest history	
IHD, %	23
Hypertension, %	40
Previous PCI, %	12
Previous CABG, %	5
Diabetes Mellitus, %	10
COPD, %	<5
Chronic kidney disease, %	<5
Characteristics related to cardiac arrest	
Place of OHCA	
Home, %	43
Public space, %	54
Other (e.g., Ambulance), %	<5
Cause of cardiac arrest	
Ischaemic heart disease, %	68
Other (cardiomyopathies, ion channel diseases, idiopathic ventricular fibrillation), %	32
Bystander witnessed cardiac arrest, %	91
Bystander performed CPR, %	95
Initial shockable cardiac rhythm, %	98
Time to ROSC, median (IQR), minutes	10 (7-16)
Treated at the ICU, %	63
Mechanical ventilated, %	61
Induced hypothermia, %	50
Length of hospital admission, median (IQR), days	12 (8-17)

ISCED: International Standard Classification of Education (21): Level 0-2: pre-primary, primary and lower secondary education, level 3 and 5: upper secondary education (high school) or vocational training and short-cycle tertiary education (there is no education corresponding to level 4 I Denmark), level 6-8: median length tertiary education, bachelor, master and PhD degrees. **IHD**: Ischemic Heart Disease, **PCI:** Percutaneous Coronary Intervention**, CABG:** Coronary Artery Bypass Graft, **COPD:** Chronic Obstructive Pulmonary Disease, **OHCA:** Out-of-hospital cardiac arrest, **CPR:** Cardiopulmonary Resuscitation, **VT/VF:** Ventricular tachycardia/ ventricular fibrillation**, ROSC:** Return of spontaneous circulation, **ICU:** Intensive Care Unit.

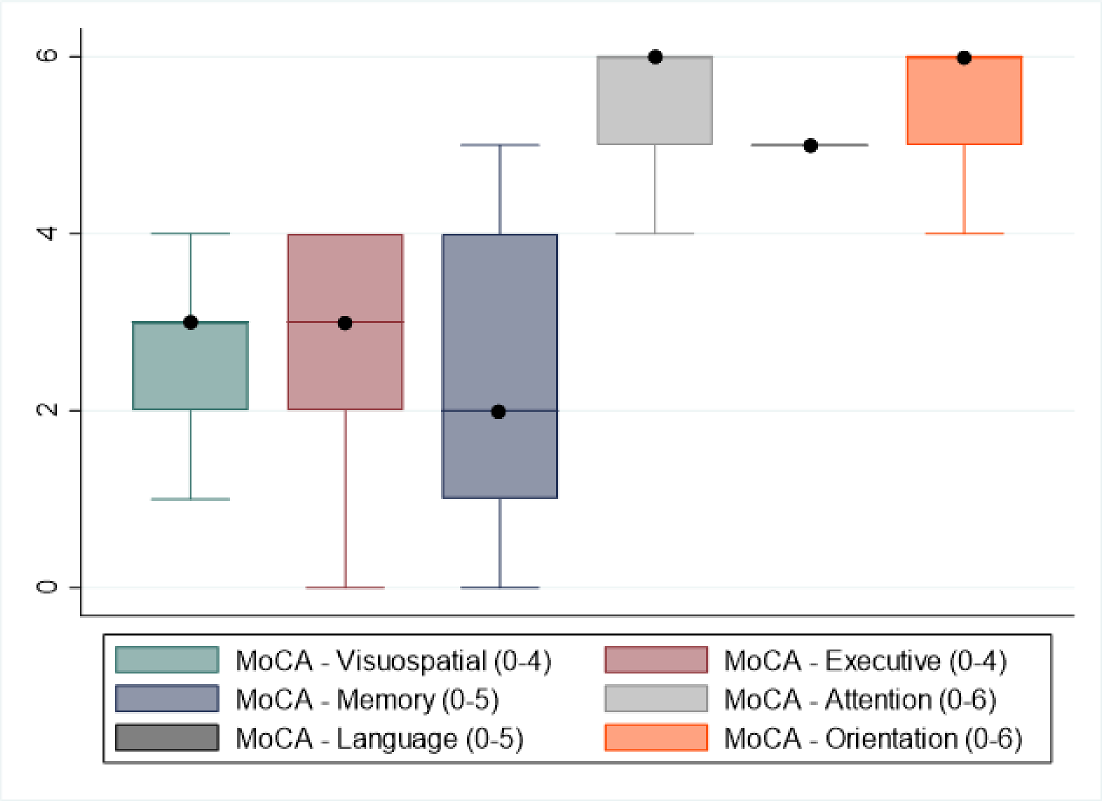

Figure 2: The cognitive screening with MoCA subdomain performances scores during hospitalisation

Median subdomain values including interquartile range (IQR) for the six cognitive domains included in the Montreal Cognitive Assessment (MoCA) score (0-30) in out-of-hospital cardiac arrest survivors (n=297)

MoCA -Visuospatial (0-4) = Cube copying (1), Clock drawing (3)
MoCA - Executive (0-4) = Trail making test (1), Phonemic fluency (words produces in a trial beginning with the letter F) (1), Verbal abstraction similarities, for example, train and bicycle=transport (2)
MoCA – Memory of novel information (0-5) = Delayed recall of a list of 5 words (5)
MoCA – Attention (0-6) = Vigilance – the letter A (1), Serial 7 subtractions (3), Forward (5 digits), backward (3 digits) (2)
MoCA – Language (0-5) = Naming (lion, hippo, camel/dromedary) (3), Repetition of complex sentences (2)
MoCA – Orientation (0-6) = Time and place (6)

Table 2: Differences between patients admitted unconscious and conscious on cognitive and psychopathological measures during hospitalisation (T1) and at three-month follow-up (T2)

	Total population		**Unconscious at admission**		**Conscious at admission**		**P**^{a}	**P**^{b}
	T1 *n*= 297	**T2** *n*=202	**T1** *n*=188	**T2** *n*=127	**T1** *n*=109	**T2** *n*=75		
Cognition								
MoCA								
Total MoCA mean ± SD	23.3 ± 4.2	N/A	22.6 ± 4.3	N/A	24.5 ± 3.7	N/A	0.0001*	
median (IQR)	24 (21-26)		24 (20-26)		25 (23-27)			
MoCA <26, n (%)	192 (65)	N/A	135 (72)	N/A	57 (52)	N/A	0.001*	
Neuropsychological test								
Non-favorable cognitive outcome	N/A	107 (53)	N/A	68 (54)	N/A	39 (52)		0.04*
Psychopathology								
HADS	*n*=269	*n*=129	*n*=170	*n*=78	*n*=99	*n*=51		
HADS-A mean (SD)	5.7 (3.9)	3.8 (4.0)	5.9 (3.8)	3.9 (4.0)	5.2 (3.9)	3.7 (4.0)	0.16	0.69
median (IQR)	5 (2-8)	3 (1-5)	5 (3-9)	3 (1-5)	5 (2-7)	3 (1-4)		
HADS-A ≥8, n (%)	68 (25)	22 (17)	50 (29)	15 (19)	18 (18)	7 (14)	0.02*	0.42
HADS-D mean (SD)	4.6 (3.7)	3.2 (3.8)	4.9 (3.7)	3.0 (3.8)	4.0 (3.6)	3.5 (3.7)	0.11	0.62
median (IQR)	3 (1-7)	2 (0-5)	4 (2-7)	2 (0-5)	3 (1-6.5)	2 (1-6)		
HADS-D ≥8, n (%)	53 (20)	19 (15)	37 (22)	11 (14)	16 (16)	8 (16)	0.22	0.95
IES-R	*n*=264	*n*=129	*n*=165	*n*=78	*n*=98	*n*=51		
IES-R mean (SD)	19.5 (13.7)	15.6 (15.0)	20.5 (14.7)	15.4 (15.0)	17.8 (12.0)	16.0 (15.2)	0.13	0.79
median (IQR)	17 (8-27)	10 (6-21)	18.5 (9-30)	10.5 (5-21)	16 (7.5-26)	10 (6-22)		
IES-R ≥30, n (%)	55 (21)	25 (19)	38 (25)	14 (18)	17 (18)	11 (22)	0.08	0.96

T1: During hospitalisation, T2: At follow-up, MoCA: Montreal Cognitive Assessment, HADS-A: Hospital Anxiety and Depression Scale – Anxiety, HADS-D: Hospital Anxiety and Depression Scale – Depression, IES-R: Impact of Event Scale-revised

[a] Test of T1 difference between the unconscious admitted group and the conscious admitted group. Student's *t*-test for continuous variables and Chi-square test for categorical variables

*b*Test of T2 differences between the unconscious admitted group and the conscious admitted group. Student's *t*-test for continuous variables and Chi-square test for categorical variables

Supplementary Materials

Table S1: Description of neuropsychological test battery

Table S1: Description of neuropsychological test battery

Cognitive domain	Test	Test description, administration, and interpretation	Primary cognitive outcome	Norm data
Episodic memory (verbal memory)	**Verbal Affective Memory Task-26 (VAMT-26)**[24]	A computerised task consisting of 26-words. Four conditions are included: 1) learning and immediate recalling 26 words on a computer screen (list A1). The A1 list with recall is repeated four times (A1 to A5), 2) short-term recalling an interference list (list B1) with 26 new words, 3) short-term recalling list A1 without seeing it (A6), and 4) long-term recalling the A1 list (A7) after a period of 30 minutes. Due to the recall period, the overall administration spanning time is 50 minutes. The tasks takes approximately 20 minutes to complete.	Condition A7 (delayed recall)	Age adjusted reference data from healthy population
Visuospatial abilities (Attention, planning, working memory)	**Rey's Complex Figure Test and recognition trial**[25]	A pen-and paper task. Four conditions are included: 1) copying the stimulus figure while viewing and drawing the figure. Subsequently both figures are removed, 2) immediate recalling and reproducing the figure from memory after a period of approximately 3) delayed recalling, after a delay of 30 minutes condition 2 is repeated, and 4) recognition trial consisting of a 4-page sheet where the patients are asked to circle the figures that were part of the original stimulus figure. Administration time is 15 minutes	Condition 3 (delayed recall) + 4 (recognition)	Norm data
Executive functioning (working memory and attention)	**The Wechsler Adult Intelligence Scale (WAIS-IV)**[27] Letter-number sequencing (LNS)	An auditive test consisting of three trials in seven sets of numbers and letters. Instructions are listening, organising, and recalling a combination of jumbled letters and numbers with increasing difficulty. The numbers has to be recited in ascending order, followed by the letters in alphabetical order. The test is stopped after three incorrect trials within the same set. Administration time is 10 minutes.		Age adjusted reference data from healthy population

Executive functioning (Working memory, attention, language, processing speed)	**The Delis-Kaplan Executive System (D-KEFS) sub-tests**[26]	Tests to assess higher level of cognitive functions (executive functions)		Age adjusted norm data from 8-89 years
	D-KEFS Trail Making Test	A series of four visual cancellation and connect-the-circle paper-tasks.The reaction time on each subtest is the outcome. Administration time is 5 minutes.	Condition 4 (switching)	
	D-KEFS Verbal Fluency Test	Compose three conditions in an oral format: Letter Fluency, Category Fluency, and Category Switching, and thereby measures fluency in the letter, category and switching between categories and problem-solving behavior. Each test has a time limit of 60 seconds and is scored in seconds per subtest. Administration time is 6-7 minutes	Condition 3 (switching)	
	D-KEFS Design Fluency Test	A nonverbal series of three tasks consisting of a paper presented row of boxes with dots to connect with four lines only – and make different designs. Besides connecting the dots and inhibiting, condition 3 also includes switching. Again, the time limit is 60 seconds per subtest which is the score. Administration Time is 7-8 minutes	Condition 3 (switching)	
	D-KEFS Colour-Word Interference Test (3+4)	Includes two baseline conditions of both inhibition and cognitive flexibility and consist of four stand-alone oral conditions: 1) naming the colour, 2) reading the words, 3) inhibit reading the words denoting colours in order to name the printed ink colour, and 4) switching back and forth between reading the conflicting words and naming the dissonant ink colours. The test is scored on completion time. Uncorrected and self-corrected errors are also measured. Administration time is 10 minutes.	Condition 4 (inhibition and switching)	

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Paper 3

Understanding the lived experiences of short- and long-term consequences on daily life after out-of-hospital cardiac arrest. A focus group study

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Understanding the lived experiences of short- and long-term consequences on daily life after out-of-hospital cardiac arrest. A focus group study

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Abstract

Aim: To explore and gain in-depth understanding of how out-of-hospital cardiac arrest survivors experience the short- and long-term consequences on daily life.

Design: A qualitative exploratory design.

Methods: A purposive sample of 32 survivors of out-of-hospital cardiac arrest. Data from six audiotaped focus group interviews were collected in either November 2018 or in March 2019. Analysis and interpretation of the transcribed texts was performed using a phenomenological-hermeneutic approach guided by Ricoeur for unfolding lived experiences.

Results: Three narratives were identified. The survivors narrated how they in the early phase after the cardiac arrest experienced: (a) 'a fragmented memory at the mercy of the system'. The analysis further showed how the participants were: (b) 'living in the shadow of anxiety and mixed feelings' and with the: (c) 'lost sense of self' up to several years after survival.

Conclusion: The participants in our study experienced distinct bodily impairments, suffering, and the lost sense of self in the return to daily life from early on to several years after resuscitation. There seem to be an urgent need for an early initiated post-arrest transitional care program led by an expert cardiac arrest nurse. In particular, the healthcare professionals need to pay attention to survivors in employment and with children living at home. Facilitated cardiac arrest peer support groups might minimize the long-term suffering, heighten the self-image, and install a new hope for the future.

Impact: To ease the post-arrest return to daily life for out-of-hospital cardiac arrest survivors it seems important that a transitional care program from the inhospital setting to the community consist of: (a) screening for and education on bodily losses at an early stage, (b) provision of support on the often prolonged emotional reactions, and (c) referring for further individual and targeted psychological and neurological follow-up and rehabilitation if needed.

KEYWORDS
cardiac arrest, daily life, focus groups, interview, lived experiences, nurse, out-of-hospital cardiac arrest, phenomenological hermeneutic

1 | INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) remains a common global medical condition as several hundreds of thousands annually are resuscitated. Up to 80% of OHCAs are caused by coronary artery disease (Porzer et al., 2017; Wong et al., 2018). The OHCA survival rate is still poor (Myat et al., 2018). In terms of morbidity and accompanying health deficits OHCA is a major public health issue as the disability-adjusted life years following adult OHCA rank third in the United States (Coute et al., 2019). As an increasing number of lay people are trained in cardiopulmonary resuscitation (CPR), and the number of and the accessibility of automated external defibrillators (AEDs) are increasing, the survival rates might improve in the coming years (Gräsner et al., 2016). In line with an expected rise in survival there is a growing awareness that a cardiac arrest is an obvious life changing event and a significant burden to the survivor (Haydon et al., 2017; Sawyer et al., 2020).

2 | BACKGROUND

Residual cognitive impairments and mental health problems frequently occur in the aftermath of a cardiac arrest (Cronberg et al., 2020; Sawyer et al., 2020). This is caused by an interruption of the blood supply to the brain during cardiac arrest, as well as responses to the acute traumatic event. These high rate disabilities are reported to negatively affect daily activities, the ability to interact in social life, the return to work (Lilja, 2017; Lilja et al., 2018) as well as quality of life after survival (Moulaert et al., 2010). Studies have investigated resuscitation experiences in a broad population of sudden cardiac arrest survivors (Brännström et al., 2018; Bremer et al., 2019; Forslund et al., 2014, 2017; Ketilsdottir et al., 2014; Sawyer et al., 2016). However, looking solely at OHCA survival, data in these studies have been collected early after the event (Forslund et al., 2014, 2017). These previous studies have found that OHCA survivors experience emotional challenges, memory loss, and an enhanced focus on what is important in life. Despite these significant insights, it is not well described, how patients adapt to, are troubled by and manage later effects in daily life after resuscitation. Moreover, most previous studies have taken a non-theoretical approach in the intertextual interpretations (Brännström et al., 2018; Bremer et al., 2019; Forslund et al., 2014; Ketilsdottir et al., 2014; Sawyer et al., 2016). To our knowledge only one study has used theory to deepen the understanding of surviving OHCA (Forslund et al., 2017). However, when it comes to investigating the return to daily life after OHCA, the literature is insufficient. As the cardiac arrest survival increases, and as there is a lack of studies that provide a more in-depth understanding of experienced consequences after survival, there is a need to explore both the short- and long-term impact of cardiac arrest on daily life more comprehensively. Thus, broader in-depth insights are needed to nuance and support the development of future tailored supportive and rehabilitative intervention programs targeted cardiac arrest survivors.

3 | THE STUDY

3.1 | Aims

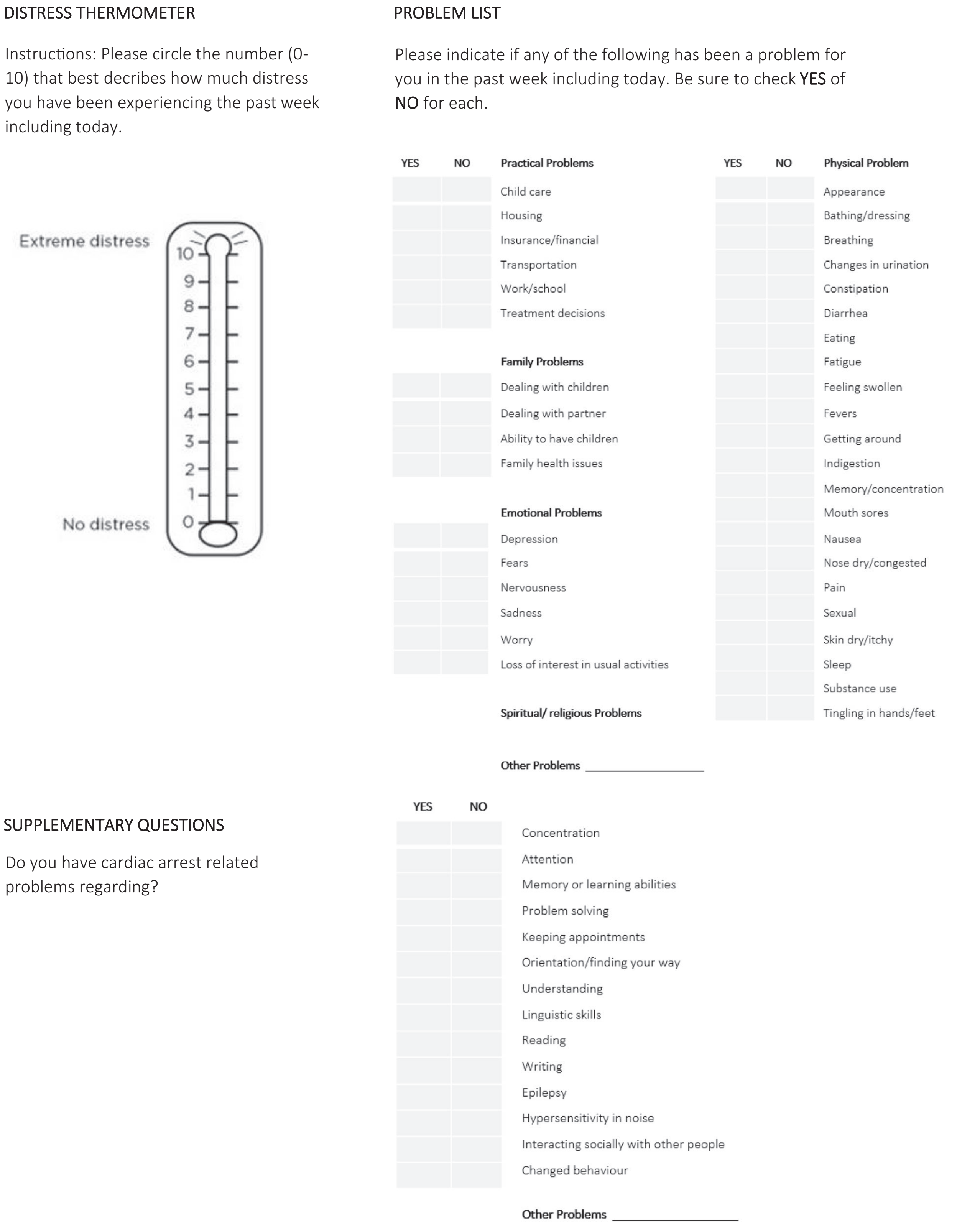
The aim of this study was to explore and gain in-depth understanding of how out-of-hospital cardiac arrest survivors experience the short- and long-term consequences in daily life. The research question was 'how do cardiac arrest survivors experience daily life and what do they emphasize as important in their return to daily life after resuscitation?'

3.2 | Design

This study had a qualitative explorative design using focus group interviews. Focus group interviewing gave the opportunity to express tacit and pre-reflective knowledge in collective discussions (Kitzinger, 2005). A phenomenological-hermeneutic approach inspired by Ricoeur's philosophy created the epistemological stance for exploring lived experiences of participants (Ricoeur, 1976).

3.3 | Participants

The Danish Heart Foundation and the Danish Cardiac Arrest Survivorship (DANCAS) network (Tang & Zwisler, 2019) invited cardiac arrest survivors to participate in a 3-day cardiac arrest rehabilitation course at the national research clinic REHPA in the Region of Southern Denmark. The original setting for enrolment at a course was a self-reported rating of own rehabilitation needs. This was inspired by the validated scale Distress Thermometer; an instrument developed to assess rehabilitation needs in cancer patients. Underpinned by the literature and knowledge from the DANCAS network expert group supplementary questions on potential problems cardiac arrest survivors may experience were added (Figure 1; Cronberg et al., 2020; Sawyer et al., 2020). Eligibility criteria for participating in a course are shown in Table 1. All 33 patients applying for a course were offered to participate either in November 2018 or in March 2019. A purposive sampling strategy was as such



DISTRESS THERMOMETER

Instructions: Please circle the number (0-10) that best decribes how much distress you have been experiencing the past week including today.

PROBLEM LIST

Please indicate if any of the following has been a problem for you in the past week including today. Be sure to check **YES** of **NO** for each.

YES	NO	Practical Problems
☐	☐	Child care
☐	☐	Housing
☐	☐	Insurance/financial
☐	☐	Transportation
☐	☐	Work/school
☐	☐	Treatment decisions
		Family Problems
☐	☐	Dealing with children
☐	☐	Dealing with partner
☐	☐	Ability to have children
☐	☐	Family health issues
		Emotional Problems
☐	☐	Depression
☐	☐	Fears
☐	☐	Nervousness
☐	☐	Sadness
☐	☐	Worry
☐	☐	Loss of interest in usual activities
		Spiritual/ religious Problems

YES	NO	Physical Problem
☐	☐	Appearance
☐	☐	Bathing/dressing
☐	☐	Breathing
☐	☐	Changes in urination
☐	☐	Constipation
☐	☐	Diarrhea
☐	☐	Eating
☐	☐	Fatigue
☐	☐	Feeling swollen
☐	☐	Fevers
☐	☐	Getting around
☐	☐	Indigestion
☐	☐	Memory/concentration
☐	☐	Mouth sores
☐	☐	Nausea
☐	☐	Nose dry/congested
☐	☐	Pain
☐	☐	Sexual
☐	☐	Skin dry/itchy
☐	☐	Sleep
☐	☐	Substance use
☐	☐	Tingling in hands/feet

Other Problems ____________________

SUPPLEMENTARY QUESTIONS

Do you have cardiac arrest related problems regarding?

YES	NO	
☐	☐	Concentration
☐	☐	Attention
☐	☐	Memory or learning abilities
☐	☐	Problem solving
☐	☐	Keeping appointments
☐	☐	Orientation/finding your way
☐	☐	Understanding
☐	☐	Linguistic skills
☐	☐	Reading
☐	☐	Writing
☐	☐	Epilepsy
☐	☐	Hypersensitivity in noise
☐	☐	Interacting socially with other people
☐	☐	Changed behaviour

Other Problems ____________________

FIGURE 1 Self-reported rating of own rehabilitation needs

applied including participants from the course. Participants were broadly represented by demographic and clinical characteristics (Table 2). The data collection was carried out until data saturation was reached.

3.4 | Data collection

Data were collected in focus groups at REHPA. As the interviews were conducted at the end of the courses, the participants were

TABLE 1 Eligibility criteria for participating in a course

Eligibility criteria
Out-of-hospital cardiac arrest survival
Willingness to convey and engage fully in a course
Needs help to find a foothold in life after cardiac arrest
Without severe neurological disabilities
Independent in activities of daily living
Able to speak and understand Danish

familiar to each other at the time of interviewing and a trusting atmosphere was created. To ensure social recognition, and thereby create a safer environment during interviewing, the participants were divided roughly into groups based on age, gender, and family type (Table 2). Based on the November 2018 interviews, and to enhance the design and programme of future cardiac arrest courses, a few questions were added to the interview guide in March 2019 about daily living. Table 3 present the interview guide with topics based on curiosity about how the participants managed their daily life and health. Previous research indicate that this patient population might experience post-arrest consequences in daily life and a concomitant decline in health and health-related quality of life (Sawyer et al., 2020). The interviews were conducted in an undisturbed room and lasted between 60-90 min. The first author had the responsibility of enabling everybody to introduce themselves, share their experiences, and carefully moving on the discussions so that all topics were covered (Table 3). The interviews were performed with an experienced assistant MM and LHT. The assistant was responsible for the audio recorder, handling of the environment conditions and logistics and was prepared to respond to unexpected interruptions. The assistant could also ask additional questions or follow-up on topics of interest. The guide helped focus the interviews and included questions on the survivors' experiences and concerns after returning to daily life (Green & Thorogood, 2014). The introductory question was ‘Can you describe how you have experienced your daily life after the cardiac arrest?’. To collect a variety of information the participants were asked to elaborate on meaningful post-arrest experiences. As the interviews progressed relevant probes were used to gain insight into issues that were raised.

3.5 | Ethical considerations

The study is registered with the reference number: 20192000-66 and conform to the basic principles of the Declaration of Helsinki. All participants gave written and informed consent to participate. The study objectives, confidentiality of data, and recording of interviews were explained to the participants prior to the interviews. Furthermore, it was explained that they could withdraw from the study at any time. During the interviews some participants experienced strong emotions (e.g., crying). These participants were offered to resume later on and debrief at the end of the interviews. Data were made anonymous by means of identification codes.

3.6 | Data analysis

The interviews were audiotaped and transcribed verbatim. Analysis and interpretation of the transcribed texts was performed using a phenomenological-hermeneutic approach inspired by Ricoeur's philosophy (Table 4). According to Ricoeur new insight of being-in-the-world can be achieved by understanding the meaning of lived experiences by utilizing an interview text and applying critical interpretation (Ricoeur, 1976). The analysis includes three main levels of textual analysis and interpretation; naïve reading, structural analysis, and comprehensive understanding. In the naïve reading the transcripts were read several times to gain an understanding of the meaning of the texts as a whole. The structural analysis organized the transcripts into meaning units. To interpret the meaning units at a deeper level and go beyond naïve understanding the aim of the structural analysis is to open up the text and pointing towards essential themes as a distanced objectivity and explanation of what is said. The process is a hermeneutic spiral moving from of what the texts say to what they talk about. The aim is to reach a comprehensive understanding of the texts by relating to theory and research. This comprehensive understanding transformed the texts to an interpreted whole where three narratives were constructed. The analytical levels in the critical interpretation are illustrated in Figure 2. The consolidated criteria for reporting qualitative research (COREQ) checklist provided guidance during the reporting of this study (Tong et al., 2007).

3.7 | Rigour

The trustworthiness was established following the criteria of Lincoln and Guba (Lincoln & Guba, 1985). Credibility was ensured, as the course created a community for the participants with a mutual understanding of one another in which they were all valued as individuals with a significant story to share (Isaksen & Gjengedal, 2000). Furthermore, the researchers had all prolonged engagements in the research setting. All interviews were conducted by the first author MKW, an experienced clinical nurse specialist within cardiology and familiar with interviewing. Credibility and dependability were increased, as the interviews were facilitated by two experienced qualitative researchers. A second set of eyes and ears increases both the total accumulation of information and the validity of the analysis (Krueger & Casey, 2015). Confirmability was ensured through a detailed audit trail of the three main levels of textual analysis and interpretation. To strengthen transferability of the findings, description of the setting, sampling strategy, and change of research questions between the two inclusion periods are provided. Substantiation of the findings and transferability was also increased by the rich inclusion

TABLE 2 Demographic and clinical characteristics of participants

Category	Focus group 1	Focus group 2	Focus group 3	Focus group 4	Focus group 5	Focus group 6	Total
Time for focus group interview	November 2018	November 2018	November 2018	November 2018	March 2019	March 2019	
Participants, *n*	5	5	7	6	4	5	32
Male: Female	3:2	3:2	6:1	3:3	4:0	5:0	24:8
Median age [IQR]	62 [53–76]	41 [40–60]	53 [44–63]	55 [51–63]	72,5 [68–83]	70 [62–76]	60 [40–83]
Median duration since OHCA (months)	12 [3–24]	18 [8–24]	14 [7–132]	12 [8–58]	57 [7–64]	16 [12–120]	16 [3–132]
Aetiology of the OHCA							
Ischaemic heart disease, *n*	3	2	6	3	4	3	21
Arrhythmia others, *n*	2	3	1	2	0	2	10
Unknown to participant, *n*	0	0	0	1	0	0	1
ICD implanted after OHCA, *n*	4	5	6	2	1	3	21
Family type							
Alone, *n*	0	0	0	1	2	0	3
Living with spouse/or partner, *n*	3	2	3	3	2	5	18
Living with spouse/or partner and children, *n*	2	3	4	2	0	0	11
Residence of region in [a]Denmark							
Capital Region of Denmark, *n*	1	1	2	1	0	4	9
Region Zealand, *n*	0	3	2	0	0	0	5
Region of Southern Denmark, *n*	0	1	2	4	2	0	9
Central Denmark Region, *n*	2	0	1	1	1	1	6
North Denmark Region, *n*	2	0	0	0	1	0	3
Education							
Elementary school, *n*	1	2	4	2	3	3	15
High school, *n*	1	2	3	2	1	2	11
≥College, *n*	3	1	0	2	0	0	6
Employment							
Before OHCA, *n*	3	5	6	6	0	2	22
After OHCA (reduced ability to work), *n*	3	4	4	5	0	1	17
Retired (8) or on sick leave (1) before OHCA, *n*	2	0	0	0	4	3	9

Abbreviation: OHCA, Out-of-Hospital Cardiac arrest.

[a] Denmark consists of five regions.

TABLE 3 Interview guide

	Open-ended questions asked to the cardiac arrest survivors
Introduction	The aim of the study is explained to participants Clarifying the roles as participants and researchers
	Can you describe how you have experienced your daily life after the cardiac arrest?
	Can you describe the impact of the cardiac arrest on your daily life?
	Can you tell about your concerns, and what have been most important for you after your cardiac arrest?
	Can you tell if and what kind of support you might have needed from your surroundings and health professionals after the cardiac arrest?
Closure	Is there anything else you would like to share before we end the interview?
	Supplementary questions for the March 2019 interviews
	Overall, how would you describe your work-life after the cardiac arrest?
	If you are a pensioner. How do you think this influence your daily life after the cardiac arrest?

of participant quotes (Lincoln & Guba, 1985; Ricoeur, 1976). The first author coded and conducted the data analysis in collaboration with the last author, an experienced researcher. Findings were discussed with all authors.

4 | FINDINGS

Six focus group interviews were conducted involving 33 out-of-hospital cardiac arrest survivors (25 men and 8 women) with a mean age of 59 (range 40–83 years) from all regions of Denmark. Divided in groups of 4–7 participants, 17 survivors took part in the interviews in 2018, and 16 survivors in the 2019 interviews. More than a third of the participants had children living at home, only three were living alone and 22 were employed before the cardiac arrest. The median time between cardiac arrest and interview was 16 months (Table 2). One male participant withdrew from the study right after the interview and was excluded. Three main narratives illuminate the participants' experiences of the hospital phase, their returning to daily life and the long-term follow-up after resuscitation: 'a fragmented memory at the mercy of the system'; 'living in the shadow of anxiety and mixed feelings'; and 'the lost sense of self'. The narratives, along with the researchers' interpretations, are presented in the following.

4.1 | Narrative (1): A fragmented memory at the mercy of the system

This narrative describes how the acute cardiac arrest phase still dominated the participants outlook in daily life. Clearly stated was experiences of partial memory loss in the time period just before and during the acute critical phase and up to weeks after hospital discharge. The remaining experiences of the acute treatment and care were fragmented and filled with perceptions of mixed sounds, colours with white light or darkness, ambience and surroundings with a high pace. Being a body that is handled at the mercy of the healthcare system is narrated as traumatic and has taken a hold (with)in the survivors. Survivors described this period as a surreal experience with shifts between experiencing nothing or being in an awake and chaotic state:

> What the heck is going on? I really felt it like that. In that way it [the cardiac arrest] is an intense and traumatic experience - an out-of-body experience. I remember that I was fighting a battle… They almost needed to lie on top of me, the ones trying to help me (8).

Being a body that is handled within the healthcare system leaves the participants with mixed feelings of frustration, lack of control, and powerlessness. Using strong words as *traumatic*, *intense*, *fight*, and

TABLE 4 Example of a structural analysis

Meaning units	Condensation/essence	Sub-theme	Theme
I do not feel self-control, only frustration. It is hard to acknowledge that nothing will be as before. I have felt like Alice in Wonderland who enters this totally new world. Who am I now and what is this? I do not know whether to go left or right or which door to open. It has been and is a huge work for me to find out who I am and what am I going to do (10). I cannot cope with as many things and continue the same pace as before. Because I work fulltime, I feel like I am banging my head against the ceiling. Not much is going on before I get confused. There are days where I can't do anything (8).	The participants experience a struggle in their return to daily life in relation to the fact that the cardiac arrest has changed who they have become compared to who they were. The participants are frustrated, confused, and searching for the sense of self.	Loss of self-control Frustration Confusion Loss of identity Helplessness	The lost sense of self

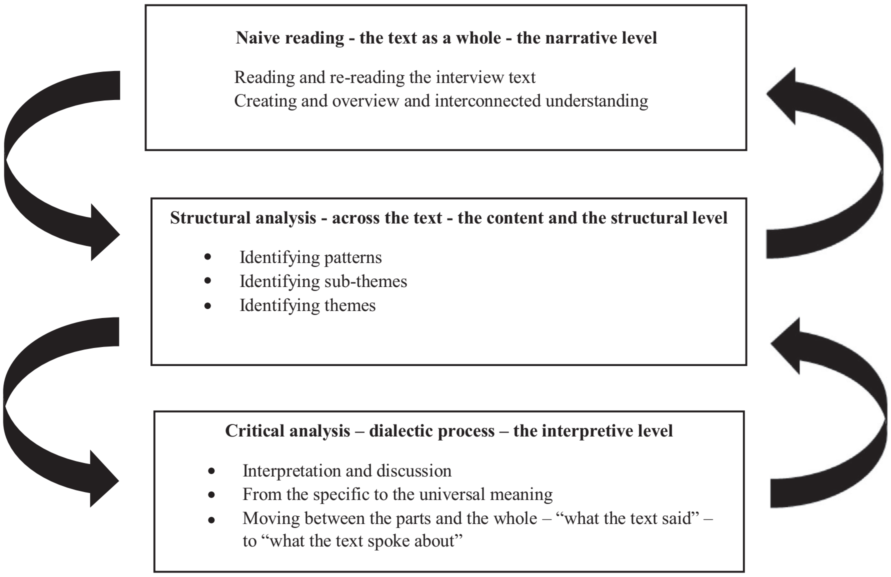


FIGURE 2 Analytical levels in the interpretation of findings

shouting emphasize that the cardiac arrest is a paramount and frightening experience. These feelings seem to hold a very strong position in the survivor's daily life narratives and are all still highly present even up to 11 years after the event.

Even though the acute management is an unpleasant and overwhelming event, the participants also highlight feelings of gratitude towards the healthcare system and their rescuers. A female participant describes how she experienced gratitude to the people who had acted in that situation: 'Ten minutes went where I was actually dead. They fought and never gave up' (4). This sense of gratitude for being saved has taken hold in the consciousness of the participants. Although they have experienced how their bodies have been handled by the healthcare professionals, they have also experienced getting their lives back.

4.2 | Narrative (2): Living in the shadow of anxiety and mixed feelings

This narrative describes how the participants are struggling with continuous emotional reactions in daily life. These challenges restrict daily life and participants are living in the shadow of anxiety and feelings of sadness and restlessness. Participants narrate how they are 'feeling down' and in 'a black hole' without joy. The implications of these feelings for the survivor are distinct meaning that common day-to-day routines are suddenly troublesome and an obstacle to managing daily life:

> It is so hard.... To be with your children and family... (crying). I have trouble going into my bedroom where it happened [cardiac arrest]. I cannot sleep in there.... I'm having a hard time with ambulances, the sound of the computer, and when people are running. It sounds like when you are having a cardiac arrest. It is in my head (7).

Not having the mental surplus to socialize with the family and avoiding reminders of the cardiac arrest dominated daily life. Several participants spoke about a sustained vulnerability as both intrusive thoughts and bodily reactions occurred frequently if reminded of the event. These reactions often first arose after discharge from the hospital but seemed to persist long term. Furthermore, feelings of insufficiency, loneliness, and guilt were present. Especially guilt and worries about the impact of the cardiac arrest and the course of the illness on the closest relatives. A male participant stated:

> The worst thing is that you wake up to a traumatised wife and kids. My biggest challenge has been to relate to my family before I have been able to relate to myself (17).

This guilt of having caused the family a major traumatic experience, weighs down on the participants and is casting a shadow over their daily life. Several close relatives had been present during the most critical phase at the hospital, perhaps also found the survivor unconscious, called for help and performed the initial cardiopulmonary resuscitation (CPR). Moreover, the participants are especially concerned about their children. In particular, if their children are at risk of having inherited the cause of the cardiac arrest; a worry they did not have before the event, but which is suddenly very present.

Overall, the participants' narratives were emotional and surrounded by a shadow of suffering and embedded sorrow and at times, the emotional chaos was overwhelming. During the interviews several participants spontaneously expressed an inadequate emotional support during the illness trajectory which they felt could have helped them in managing daily life. What the participants expressed was missing was a support to help deal with individual challenges, to talk problems through and to deal with hereditary issues. Such emotional issues like talking about death and related thoughts about death were expressed as very sensitive to bring up around close relatives. Therefore, the participants often chose not to burden relatives in this regard. Instead talking to peers was emphasized as a possible and valuable supplement to manage daily life.

4.3 | Narrative (3): The lost sense of self

This narrative describes the long-term experiences of having 'lost yourself' after the cardiac arrest. The struggle to hold on to some kind of normality and balance within the changed life was frustrating and confusing, especially among the younger and middle-age participants who were still employed:

> I do not feel self-control, only frustration. It is hard to acknowledge that nothing will be as before. I have felt like Alice in Wonderland who enters this totally new world. Who am I now and what is this? I do not know whether to go left or right or which door to open. It has been and is a huge work for me to find out who I am and what I am going to do (10).

As illustrated in the quote above, it was difficult to come to the realization that nothing would be as before, and that the participant's life situation had changed by the event. Before the cardiac arrest this woman was physically active, both in her leisure time, at the house, at work, and with sports. The feeling of losing this basis of her identity, her sense of self and how others pictured her was described as difficult. Other participants also narrated about a life before the cardiac arrest where work was a substantial part of their identity. In particular, the search for acceptance from colleagues within a certain working community subsequently became crucial for returning to daily life:

> This is what is important and what we live for now, when we work. Respect from our colleagues. I was afraid that I would be put in a corner. But they still need me and what I do (6).

A persistent challenge for the participants was experiences of extreme and long-term fatigue accompanied with concentration difficulties, lack of focus and mental resources, short-term memory problems, headaches and feeling irritable and irrational. These impairments had an impact on the individual's self-perception. The participants described how they felt losing parts of themselves and their identity:

> I work fulltime. Not much is going on before I get confused and I feel like I am banging my head against the ceiling. I cannot cope with as many things and continue the same pace as before. There are days where I can't do anything (8).

This overwhelming feeling of fatigue disrupts daily life leaving the participants in a powerless position and with a call for help. Contrary to this participant a few others received support and guiding to help manage their acquired impairments:

> …my neuro psychologist tells me that I have to adapt to daily life and try not to be worn out. It means that I need breaks when one hour has passed. It is hard, but if I don't do this, I will be totally worn out after three hours (9).

The participants unanimously agreed that the sooner a professional helping hand was initiated, the disrupted and altered daily life was somewhat easier to deal with.

5 | DISCUSSION

In the following, we elaborate on what might be at stake for survivors of a cardiac arrest, derived from the identified themes. Selected aspects of theory are used to interpret the findings to achieve a further, deeper, and comprehensive understanding of the participants' lived experiences (Ricoeur, 1976).

During the acute phase of the cardiac arrest, participants both experienced and lived through their bodies. Looking back at the hospitalization, the experiences were fragmented, traumatic and with glimpses of a body being handled within the mercy of the healthcare system. Being a body that is handled by others mercy may evoke experiences of alienation and as a threat to one's self with a risk of suffering. This changed sense of own body might though be formed by the responsive approach from others (Storli, 1999). In a medical approach to the body, Lock and Ngyen state that the clinicians inevitably focus on the physical body in an acute critical situation of a cardiac arrest. For the affected person this standardized medicalization focusing on the body can seem reductionistic. However, survival is the main target and the most important cardiac arrest outcome (Lock & Ngyen, 2010). Despite this fact, our study showed that in the medicalized environment, during treatment and care, the state of mind of our study participants was of a more comprehensive nature underpinned by feelings of a changed body and fear as well as lack of control and out-of-body experiences. As such the participants spoke about their bodies as more than just physical boxes. Løvås has described how the body during critical illness might be experienced without boundaries and as unrecognizable (Løvås, 1988). However, such accompanying consequences of a cardiac arrest might not be realized at hospital discharge. Recent research although reported that addressing bodily changes in a stable but early phase after the event may help the patient in an acceptance of the new situation and the consequences of bodily impairments (Sawyer et al., 2020).

Our study further illuminated how the participants were living a daily life in the shadow of anxiety and mixed feelings from early on to several years after the cardiac arrest. Burdened by emotional reactions they expressed how they did not have the mental surplus socializing with their families. Health issues is reported to be an area of significant concern for survivors of OHCA (Haywood &

Dainty, 2018; Wilder Schaaf et al., 2013). A pronounced issue for the participants in our study was the feeling of guilt over having inflicted a traumatic experience on the family which casted a shadow over their life. Other studies report difficulties in meeting such emotional needs of survivors (Haydon et al., 2017; Haywood & Dainty, 2018; Lilja et al., 2018). From a caring perspective, nurses must minimize and relieve suffering during a course of illness. According to Morse two broad and divergent behavioural conditions are present in suffering; *enduring* where emotions are suppressed and *suffering* where emotions are released (Morse, 2001). Enduring persists while the suffering is still pre-reflective and unspoken, and all energy is used to maintain control while adapting to this new situation. Enduring can induce long-term anxiety and depression. Emotional suffering is, however, the opposite and is a condition where suffering is acknowledged and expressed. Emotional suffering is often characterized by feelings of sorrow and sadness, as the individual comes to the realization of what is lost and what this means in daily life (Morse, 2001). For cardiac arrest survivors who are living in the shadow of anxiety and mixed feelings, and an acknowledgement of a new daily life, Morse emphasizes the significance of nurses being empathic, asking about suffering, meeting patients in articulating worries and taking action on feelings and thoughts to support these people (Morse, 2001). Participants in our study speak about post-arrest suffering in daily life up to 11 years. This suffering is a threat to the well-known daily life. Therefore, it has to be expressed and acknowledged together with finding time and space to live through the suffering (Eriksson, 1995; Morse, 2001). By focusing on psychosocial well-being (Sawyer et al., 2020), the individual might be ready to move on with a reorientation and new meaning in life.

Participants in our study experienced a lost sense of self after the cardiac arrest. According to Bury 'illness interrupts the expectations and plans that individuals hold for the future' (Bury, 1982, p. 169) and 'requires a fundamental rethinking of the person's biography and self-concept' (Bury, 1982, p. 177). Experiences related to the cardiac arrest were for our participants indeed a disruptive event. Facing daily life with acquired impairments such as fatigue, concentration difficulties, and short-term memory problems resulted in an altered daily life where the survivors felt being alone with their interrupted biographical experiences. We found that the younger participants, who were employed and with children living at home, were trying to ignore, minimize, and struggle against the fatigue and impairments for a long time. This resulted in a feeling of 'banging the head against the ceiling'. As stated by Charmaz, people may ignore a certain illness and additional consequences if they, for example, want to keep a certain job (Charmaz, 1995). Through this theoretical lens our findings emphasize that especially younger cardiac arrest survivors need special attention, as they struggle against impairments and ignore them for a long time in an effort of returning to their previous daily life. As illuminated in our study, this strategy, however, has consequences leaving the survivors in a protracted powerless position. Developing education programs and referring for individualized and targeted psychological and neurological follow-up and rehabilitation is therefore urgently needed.

5.1 | Limitations

We collected data from a relatively large number of OHCA survivors aged from 40–83 years with a majority of men, from all regions of Denmark, and from all groups of society. As two thirds of cardiac arrest patients in Denmark are male (Wissenberg et al., 2014), with a wide age range, this sample might thereby reflect the population in general, making transferability of findings possible. Participants were, however, recruited from a population of OHCA survivors who themselves chose to sign up for the course. The sample in this study might therefore reflect participants who had more resources to narrate about their experiences and act upon their situation. Moreover, a potential study limitation is the generous timespan of 3 months to 11 years from cardiac arrest to time of interviewing. This means that some variations are expected in how the participants experience the consequences on daily life after OHCA. On the other hand, this study explore what the participants emphasize as important from early on to long term in their return to daily life after resuscitation.

6 | CONCLUSION

Characterized by distinct bodily impairments, mental suffering, and the lost sense of self, patients surviving OHCA experience a disrupted daily life from early on to several years after resuscitation. The findings suggest that the role of a post-arrest healthcare team is emphasized as significant to the return to daily life after resuscitation. In particular, the findings highlight that a transitional care program led by a coordinating expert cardiac arrest nurse between the inhospital setting and the community might be the needed organizational link to reconcile with early bodily losses and accompanying prolonged emotional reactions, suffering and a lost sense of self. To ease the return to daily life it seems important that screening for and education on bodily losses is given at an early stage, support is provided on the emotional reactions, and referral for further psychological and neurological follow-up and rehabilitation is addressed in a systematic manner. In particular, for the survivors in employment and with children living at home the cardiac arrest seem to have a considerable impact on the experiences of the return to daily life in the aftermath after resuscitation. Besides the important role of the transitional healthcare professionals, facilitated peer support groups might provide a perspective of shared experience and emotional support among cardiac arrest survivors that minimize the long-term suffering and heighten the self-image which instill a new hope for the future and improve the return to daily life after resuscitation.

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CONFLICTS OF INTEREST

No conflict of interest has been declared by the authors.

AUTHOR CONTRIBUTIONS

MKW, SKB, LHT, DSS, CH, and MM made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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