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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract:

Aims: Explore aspects of health-related quality of life (HRQoL) and caregiver burden after out-of-hospital cardiac arrest (OHCA). Specific aims were: **I)** Describe survivors' HRQoL at 6 months and differences related to sex, age, and population norms. **II)** Describe caregiver burden and HRQoL and their associations with survivor' cognitive function, and compare OHCA caregivers with a ST-segment elevated myocardial infarction (STEMI) controls. **III)** Evaluate psychometric properties of EQ-5D-5L in OHCA survivors. **IV)** Explore longitudinal health status, and the relationship with temperature management, pre-arrest factors, and life satisfaction.

Methods: I) Cross-sectional, post-hoc analyses of 442 survivors from the Target Temperature Management 33 °C versus 36 °C after Out-of-Hospital Cardiac Arrest trial (TTM-trial) at 6 months. **II)** Cross-sectional study with 272 OHCA caregivers and 108 STEMI caregivers from the TTM-trial cognitive substudy at 6 months. **III)** Cross-sectional, post-hoc analyses of 783 survivors from the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2-trial) at 6 months. **IV)** Longitudinal analyses of 836 survivors from the TTM2-trial at 6 and 24 months.

Results: I) Overall HRQoL approximated population norms, but a substantial proportion reported impaired role functioning. Female survivors reported poorer HRQoL than males and sex-adjusted norms. Older survivors reported more physical problems but better mental health than younger survivors. **II)** Survivor cognitive impairment was associated with higher caregiver burden and lower HRQoL. Caregiver burden was also related to survivors' functional outcome, comorbidity, and cohabitation. Burden and HRQoL did not differ between OHCA and STEMI caregivers. **III)** Support for a unidimensional latent structure of EQ level sum score (EQ LSS) was found. A high floor effect was observed. Associations between EQ-5D-5L and functional dependency supported construct validity. **IV)** Neither overall health nor any EQ-5D-5L dimension differed between hypothermia and normothermia groups. Comorbidity was strongly associated with mobility problems. Age, biological sex, and marital status were associated with Anxiety/Depression. Group-level EQ-5D-5L scores showed no significant change from 6 to 24 months. Based on EQ VAS, 27% improved, 26% declined, and 47% had no clinically relevant change. Life satisfaction related most to Anxiety/Depression.

Conclusions: OHCA survivors often recover to near-population health, but a substantial minority report persistent physical, cognitive, and psychological problems that also affect caregivers. By evaluating the psychometric performance of EQ-5D-5L, highlighting caregiver impact, and complementing health status with life satisfaction, this thesis fills key knowledge gaps and strengthens the evidence base for the use of generic PROMs in OHCA research.

Key words: Heart arrest; Health-Related Quality of Life; Patient reported outcomes; Psychometrics; Psychological Well-Being

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To Stella, Klara, and Isak

'Run when you can, walk if you have to, crawl if you must;
just never give up.'
– Dean Karnazes

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II. **Bohm M**, Cronberg T, Årestedt K, Friberg H, Hassager C, Kjaergaard J, Kuiper M, Nielsen N, Ullén S, Undén J, Wise MP, Lilja G. Caregiver burden and health-related quality of life amongst caregivers of out-of-hospital cardiac arrest survivors. *Resucitation*. **2021**;167:118-127.

III. **Bohm M**, Årestedt K, Ullén S, Nielsen N, Dankiewicz J, Friberg H, Blennow Nordström E, Cariou A, Jakobsen JC, Grejs AM, Haenggi M, Hammond NE, Heimburg K, Keeble TR, Leithner C, Rylander C, Undén J, Wise MP, Cronberg T, Lilja G. Psychometric evaluation of EQ-5D-5L in OHCA survivors from the TTM2 trial: a post hoc analysis. *Resucitation Plus*. **2025**;24:1-10. https://doi.org/10.1016/j.resplu.2025.100994

IV. **Bohm M**, Andertun S, Ullén S, Nielsen N, Dankiewicz J, Friberg H, Levin H, Blennow Nordström E, Jakobsen JC, Heimburg K, Bělohlávek J, Cariou A, Haenggi M, Hammond NE, Hovdenes J, Keeble TR, Kirkegaard H, Leithner C, Rylander C, Thomas M, Undén J, Wise MP, Årestedt K, Cronberg T, Lilja G. Health status at 6 and 24 months after out-of-hospital cardiac arrest: findings from the TTM2 trial. Unpublished manuscript.

Abbreviations

AHA	American Heart Association
CCI	Charleson Comorbidity Index
CFA	confirmatory factor analysis
CFS	Clinical Frailty Scale
CI	confidence interval
COSCA	core outcome set for cardiac arrest
CPR	cardiopulmonary resuscitation
CTT	classical test theory
DIF	differential item functioning
EEG	electroencephalography
EMS	emergency medical services
EQ LSS	EQ level sum score
HRQoL	health-related quality of life
ICC	intraclass correlation
ICF	International Classification of Functioning, Disability, and Health
ICU	intensive care unit
IHCA	in-hospital cardiac arrest
IQR	interquartile range
mCCI	modified Charlson Comorbidity Index
MCID	minimal clinical important difference
MCS	Mental Component Summary
MoCA	Montreal Cognitive Assessment
mRS	modified Rankin Scale
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PCAS	post-cardiac arrest syndrome
PCS	Physical Component Summary
PRO	patient-reported outcome

PROM	patient-reported outcome measure
RCT	randomised controlled trial
ROSC	return of spontaneous circulation
SD	standard deviation
SDC	smallest detectable change
SDMT	Symbol Digit Modalities Test
SEM	standard error of measurement
SET	Self-Evaluated Transition
SRM	standardised response mean
STEMI	ST-segment elevation myocardial infarction
TTM-trial	Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest trial
TTM2-trial	Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial
WLST	withdrawal of life-sustaining therapies
ZBI-22	22-item Zarit Burden Interview

Abstract

Aims: Explore aspects of health-related quality of life (HRQoL) and caregiver burden after out-of-hospital cardiac arrest (OHCA). Specific aims were: **I)** Describe survivors' HRQoL at 6 months and differences related to sex, age, and population norms. **II)** Describe caregiver burden and HRQoL and their associations with survivor' cognitive function; and compare OHCA caregivers with a ST-segment elevated myocardial infarction (STEMI) controls. **III)** Evaluate psychometric properties of EQ-5D-5L in OHCA survivors. **IV)** Explore longitudinal health status, and the relationship with temperature management, pre-arrest factors, and life satisfaction.

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Populärvetenskaplig sammanfattning

Bakgrund

När ett plötsligt och oväntat hjärtstopp inträffar utanför sjukhus är det ett akut och livshotande tillstånd. En vanlig orsak är när hjärtats elektriska system slutar att fungera normalt och hjärtat slutar pumpa ut blod effektivt eller inte alls. När inget blod cirkulerar i kroppen blir den som drabbats snabbt medvetslös och slutar att andas. Utan snabb hjärt-lungräddning (HLR) är chansen att överleva liten.

Den blodcirkulation som åstadkoms genom HLR kan minska omfattningen av skador i hjärnan och resten av kroppen som uppstår på grund av syrebristen under hjärtstoppet. Därför är snabbt påbörjande av effektiv HLR och snabb defibrillering med hjärtstartare så viktig. Under de senaste åren har fler kunnat räddats till livet tack vare tidigt larm och snabbt påbörjad HLR. Ökade utbildningsinsatser, ökad utbredning av tillgängliga hjärtstartare i samhället samt införandet av frivilliga livräddare har också förbättrat överlevnaden. En stor andel av hjärtstopp utanför sjukhus sker i det egna hemmet, men kan också ske i en offentlig miljö eller på arbetsplatsen.

Bara i Sverige drabbas ungefär 6000 människor varje år av hjärtstopp utanför sjukhus och där HLR påbörjas. Trots det är det ungefär bara en av tio drabbade som överlever och globalt sett är det en av de allra vanligaste dödsorsakerna. Under den tidiga fasen efter återupplivningen är många fortfarande medvetslösa och vårdas på en intensivvårdsavdelning.

Nedsatt kognitiv funktion, som minnes- och koncentrationssvårigheter, är vanligt hos överlevare efter hjärtstopp, men eftersom de ofta är lindriga kan de vara svåra att upptäcka omedelbart hos de drabbade. Kognitiva problem är bland annat förenat med symtom på ångest och depression. Vardagslivet och delaktighet i samhälle kan också påverkas, inklusive möjlig återgång till arbetslivet. Det är inte heller ovanligt att den som överlever ett hjärtstopp upplever en svår trötthet och orkeslöshet. Detta kan sammantaget leda till nedsatt livskvalitet och välbefinnande.

Även kan närstående påverkas, både kort- och långsiktigt. Det är många gånger en traumatisk upplevelse för den som bevittnat hjärtstoppet och kanske själv påbörjar hjärtlungräddning. Därför behöver vi förstå hur människor mår och fungerar efteråt.

Ett sätt är att mäta så kallad hälsorelaterad livskvalitet. Som teoretiskt koncept saknar det en enhetlig och tydlig definition, men kan förenklat förklaras som de aspekter av en individs livskvalitet som är relaterade eller påverkas av olika hälsodimensioner, till exempel fysisk, mental och social hälsa.

Tidigare forskning har ofta använt patientrapporterade utfallsmått för att kunna mäta hälsorelaterad livskvalitet efter hjärtstopp, men vi vet mindre om hur väl dessa instrument fungerar just i gruppen med överlevare och närstående. Hur närstående skattar deras upplevelse av börda av att vara närstående och kopplingen till kognitiv funktion situation har också studerats i mindre omfattning. Dessutom vet vi för lite om hur självskattad hälsa utvecklas under de första två åren efter hjärtstoppet samt vilka faktorer som hänger ihop med förbättring eller försämring över tid.

Avhandlingens övergripande mål är att utforska olika aspekter av hälsorelaterad livskvalitet, självskattad hälsa och närståendebörda efter hjärtstopp utanför sjukhus. Målet är även att testa hur väl olika mätinstrument fungerar i denna grupp samt följa hur överlevares självskattade hälsa utvecklas från 6 till 24 månader.

Metod

Avhandlingen består av fyra delarbeten. Det första delarbetet baserades på insamlade data från en stor internationell hjärtstoppstudie, TTM studien, som undersökte om temperaturkontroll vid 33 °C jämfört med 36 °C ledde till bättre överlevnad samt minskade hjärnskador. Publicerade resultat visade att det inte fanns någon skillnad i övergripande livskvalitet mellan temperaturgrupperna. Därför gjordes inga fortsatt analyser av detaljerad livskvalitet mellan temperaturgrupperna. I det första delarbetet analyserades hur 442 deltagare skattade sin hälsorelaterade livskvalitet vid 6 månader efter hjärtstoppet och om det fanns skillnader mellan åldersgrupper, mellan män och kvinnor, och jämfört med en normalbefolkning.

Det andra delarbetet baseras på TTM:s kognitiva substudie, som undersökte kognitiv funktion efter hjärtstopp mer detaljerat. För att bedöma om det går att skilja på kognitiv funktionsnedsättning efter hjärtstopp från en möjlig redan underliggande kognitiv svikt, användes en kontrollgrupp av patienter med hjärtinfarkt. Den här gruppen valdes för att den har liknande risker för hjärt-kärlsjukdomar, men inte riskerade en hjärnskada eftersom de inte har drabbats av hjärtstopp. Både hjärtstoppsöverlevarna och kontrollgruppen ombads att ta med sig en närstående till uppföljningen vid 6 månader efter den inträffade hjärthändelsen. I det här delarbetet deltog 272 närstående till hjärtstoppsöverlevare och 108 närstående till hjärtinfarktpatienter. Alla närstående fick svara på samma enkät om vilken börda de upplevde som närstående samt deras hälsorelaterade livskvalitet.

Hjärtstoppsöverlevarna kategoriserades också utifrån deras kognitiva funktion för att närmare kunna analysera sambandet mellan kognitiv funktion och upplevelsen av börda och livskvalitet hos närstående.

Tredje och fjärde delarbetena bygger på en annan stor internationell hjärtstoppsstudie, TTM2 studien, som jämförde temperaturkontroll vid 33 °C jämfört med att upprätthålla normal kroppstemperatur och tidig behandling av feber. Vid både 6 och 24 månader fick överlevarna fylla i ett självskattningsinstrument om deras upplevelse av hälsa. Det tredje delarbetet utvärderade om instrumentets mätegenskaper, hos 783 av överlevarna vid 6 månader, är tillräckligt tillförlitliga för att instrumentet ska användas i den här målgruppen. I fjärde delarbetet följdes 836 överlevare vid 6 och 24 månader och fokuserade på hur överlevares självupplevda hälsa förändras över tid.

Resultat

Många överlevare skattade sin hälsorelaterade livskvalitet 6 månader efter hjärtstoppet nära en genomsnittlig normalbefolkning. Samtidigt rapporterade en betydande andel kvarstående begränsningar i att utföra vardagliga aktiviteter och arbete på grund av både fysiska och/eller emotionella problem. Kvinnor rapporterade generellt lägre livskvalitet, både jämfört med män och könsjusterade normvärden. Äldre hade fler fysiska besvär men skattade ofta sin mentala hälsa högre än yngre överlevare. När överlevaren hade kognitiva svårigheter var upplevelse av börda för närstående större och deras livskvalitet lägre. Även nedsatt funktionsnivå och underliggande sjukdomar hos överlevaren, samt om närstående och överlevaren bodde tillsammans hängde samman med upplevelsen av ökad börda. Nivåerna av börda och livskvalitet skilde sig inte mellan anhöriga till hjärtstoppsöverlevare respektive hjärtinfarktpatienter.

Det fanns metodologiska stöd för att använda ett av de vanligaste instrumenten för att mäta självskattad hälsa i den gruppen. Det fanns tydliga samband mellan nedsatt självskattad hälsa och både nedsatt funktionsnivå och kognitiva problem. Samtidigt hade instrumentet vissa svagheter. Till exempel skattade en stor andel bästa möjliga hälsa. Det begränsar instrumentet att kunna upptäcka små förändringar och skilja mellan personer med få hälsoproblem, vilket minskar trovärdigheten av instrumentets mätegenskaper.

Att ha tidigare underliggande sjukdomar var tydligt kopplad till problem med rörlighet, medan ålder, kön samt civilstånd hade framför allt samband med upplevelse av ångest och depression vid 6 månader. Generellt sett förändrades överlevarnas självskattade övergripande hälsa lite mellan 6 och 24 månader, men på individnivå förbättrades ungefär var fjärde, en lika stor andel försämrades, och knappt hälften hade oförändrad hälsa.

Livstillfredsställelse hade starkast samband med upplevelse av ångest och depression, och sammantaget var sambanden mellan självskattade hälsa och livstillfredsställelse måttliga, vilket visar att de delvis fångar olika aspekter av hur man mår och därför kompletterar varandra.

Slutsatser

Även om många överlevare skattar sin livskvalitet och hälsa nära en normalbefolkning, har en betydande andel kvarstående fysiska, kognitiva och emotionella besvär som påverkar både deras vardag och rollfunktion, vilket också påverkar deras närstående negativt. Vanligt använda instrument för att mäta självskattad hälsa är användbara i den här gruppen. För att fånga en så komplett bild som möjligt av olika problem efter hjärtstopp och för att kunna hitta dem som behöver mest stöd och rehabilitering, behöver de kompletteras med andra instrument. Livstillfredsställelse ger till exempel ett viktigt perspektiv utöver självskattad hälsa. Bilden av överlevares självskattade hälsa och hur den utvecklas över tid efter hjärtstopp är komplex och följer inte ett enhetligt mönster.

De kliniska implikationerna är att eftersom nedsatt funktionsnivå och kognitiva problem är starkt kopplade till självskattad livskvalitet och hälsa samt upplevelsen av börda hos närstående, visar avhandlingen på vikten av tidig identifiering av vanliga problem för att kunna sätta in rätt stöd och rehabilitering. Särskild uppmärksamhet behövs för yngre överlevare, kvinnor och personer med underliggande sjukdomar. Kopplingarna mellan tidigare underliggande sjukdomar och nedsatt rörlighet visar vidare på vikten av fysisk aktivitet både för att minska risken för hjärt-kärlsjukdomar samt det riktade rehabiliteringsbehovet till den här gruppen. Närstående behöver också erbjudas information och stöd, speciellt de som är närstående till överlevare med svårare kognitiva problem eller funktionsnedsättningar. När svåra problem identifieras kan personen behöva remitteras vidare till mer specialiserad rehabilitering efter hjärtstoppet, för att underlätta återgången till ett så normalt liv som är möjligt för både överlevare och närstående.

Preface

I always knew I wanted to work with critically ill patients in an intensive care setting since the beginning of my undergraduate nursing education in the early 2000s. However, it wasn't until after I completed my first-year master's program and became a critical care registered nurse in 2011 that I finally began working in an intensive care unit (ICU).

Throughout my professional career, I have continuously sought deeper knowledge about what happens to the patients I have cared for after they leave the ICU, and how to optimize their transition to the ward. Early on, I explicitly expressed my interest in developing more effective health care systems and improving patient outcomes, alongside a desire for further academic education.

Eventually, I took part in a task force dedicated to enhancing the transition from ICU-to-ward. The task force developed a care bundle to increase patient safety throughout hospitalisation. A significant outcome of this initiative was establishing a liaison nurse role, inspired by successful international models, which reduced ICU readmissions and improved patient satisfaction for previously critically ill patients.

Shortly after the completion of this initiative, I was asked if I would be interested in co-authoring a paper analysing health-related quality of life after out-of-hospital cardiac arrest. Having cared for patients enrolled in a groundbreaking international trial at the time, the opportunity seemed exciting and meaningful. Without much hesitation and fully comprehending what it entailed, I naively accepted, not yet grasping the implications of the academic work. Around this time, the question of pursuing a PhD arose. Although obtaining a doctorate was alluring, through the previous work of colleagues, friends, and family, I dismissed this idea. Yet, this conversation planted a small seed of possibility—that perhaps, even I could achieve such a goal. Soon, however, I recognized significant gaps in my knowledge, particularly in statistical analysis, prompting me to pursue a second-year master's degree to be able to continue and finish the project.

After I had graduated the master's program, I applied for and was appointed as a liaison nurse, facilitating patient transitions and performing early follow-ups on the ward. This role deepened my understanding of the difficulties faced by patients after prolonged critical illness, including delirium, psychological distress, and ICU-acquired muscle weakness, as symptoms of post-intensive care syndrome.

Simultaneously, I finalised the publication of the initial paper in a renowned international journal—a personal victory. Upon achieving this milestone, I felt a mixture of pride, relief, and newfound curiosity. I wondered, 'Now what? Is this really all?' When the possibility of pursuing a PhD arose once more, I realised this was an opportunity I could not dismiss, and I felt compelled to accept this challenge.

Thus, my journey toward this PhD thesis began. As I look forward, acknowledging the uncertainties but embracing the possibilities that lie ahead…

> *The Road goes ever on and on*
> *Down from the door where it began.*
> *Now far ahead the Road has gone,*
> *And I must follow, if I can,*
> *Pursuing it with weary feet,*
> *Until it joins some larger way,*
> *Where many paths and errands meet.*
> *And whither then? I cannot say.*
>
> —J.R.R. Tolkien, *The Fellowship of the Ring*

Background

Cardiac arrest

Cardiac arrest is typically described as the sudden stop of effective heart function, recognised clinically by the absence of signs of circulation [1]. When the heart stops pumping blood effectively, it results in a rapid loss of consciousness, absence of normal breathing, and other signs of circulation.

Cardiac arrests are typically categorised based on the location of the incident, as either an out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA), if occurring during a hospital admission. This distinction is needed because of differences in the underlying causes of the arrest, response times to initiation of CPR, availability of immediate interventions, and patient demographics [2].

OHCA remains a major global health problem with high mortality rates [3]. Survivors can experience functional impairments, cognitive deficits, psychological distress, and reduced health-related quality of life (HRQoL). The impact of OHCA extends beyond the patient, it also profoundly affects the family, often referred to as co-survivors, which underscores the need to consider outcomes beyond survival alone [4, 5].

The attention has shifted from simply increasing survival to also understanding and improving long-term outcomes. Surviving a cardiac arrest can affect multiple health dimensions and functioning, necessitating comprehensive rehabilitation strategies to optimise recovery and well-being for survivors. Furthermore, the increasing recognition of psychosocial challenges experienced by co-survivors highlights the need to also address caregiver burden [4].

Understanding long-term outcomes of both survivors and co-survivors and how they can be improved have gained increasing recognition as important beyond survival alone.

Presumed cause of OHCA

One of the defining characteristics of sudden cardiac arrest is its highly time-dependent nature. In many cases, the underlying cause is not known during resuscitation efforts. As a result, a simplified classification commonly applied, is distinguishing between presumed cardiac or unknown causes and non-cardiac causes. The most frequent underlying cause of OHCA among patients who achieve return of spontaneous circulation (ROSC) and are admitted to hospital, is either chronic or acute coronary artery disease [3]. A common mechanism is rupture of an atherosclerotic plaque, leading to myocardial ischemia. If perfusion is not restored quickly, it may result in a myocardial infarction, which in some cases presents as a ST-segment elevation myocardial infarction (STEMI) [3, 6].

Coronary artery disease is a common cardiac cause of OHCA.

Epidemiology and survival after OHCA

The global incidence rates of OHCA varies widely, ranging from approximately 30 to 100 incidents per 100,000 inhabitants per year [2, 3]. Despite improvements in emergency response systems and resuscitation practices, overall survival remains low, averaging around 10% [7]. Although, of those who survive to hospital discharge, long-term survival is relatively favourable, with survival rates of 64% 10 years after OHCA [8].

While OHCA is one of the leading causes of mortality worldwide, long-term survival among those who survive to hospital discharge are 64% at 10 years.

The chain of survival

The chain of survival includes key links of how to improve chances of survival, by early recognition and call for help, early high-quality cardiopulmonary resuscitation (CPR), early defibrillation, and advanced cardiac life support. The concept was originally developed by the American Heart Association (AHA) in 1991 and has been further revised with additional links added, where the last 6th link is recovery, emphasising optimal support and rehabilitation [9]. The critical role of bystander CPR and defibrillation have especially been emphasised for improving the chances of survival [8, 10].

The concept of chain of survival emphasises that all links needs to be optimised to increase the chance of survival.

Demographic and clinical determinants of outcome after OHCA

In addition to cardiac arrest specific factors such as initial rhythm, bystander CPR, and emergency medical services (EMS) response times—several demographic and clinical characteristics also influence survival and recovery after OHCA.

Individual characteristics play an important role in outcome after OHCA. Factors such as age, biological sex, socioeconomic status, and pre-arrest comorbidities have been shown to affect both survival and neurological prognosis [6, 11, 12].

Clinical frailty, defined as a multidimensional syndrome of reduced physiological and functional reserves in older adults [13], leads to an increased vulnerability and has been linked to worse outcomes after cardiac arrest [14, 15].

Post-cardiac arrest syndrome

The pathophysiology of a cardiac arrest involves the loss of cardiac output, leading to global cerebral and multiorgan ischemia/hypoxia. The subsequent reperfusion occurring after ROSC, initiates inflammatory and metabolic responses collectively termed post-cardiac arrest syndrome (PCAS) [16]. There are four interrelated components that encompasses PCAS: brain injury, cardiac dysfunction, systemic inflammatory response, and ongoing underlying pathologies [16].

Understanding PCAS and treating the underlying cause of the cardiac arrest is critical to reduce secondary injuries and improve long-term outcomes [17]. While, the brain injury is a key factor determining long-term outcomes following OHCA [18], it arises from overlapping mechanisms that remain poorly understood [19].

Post-cardiac arrest syndrome encompasses four interrelated components: brain injury, cardiac dysfunction, systemic inflammatory response, and ongoing underlying pathologies.

Post-cardiac arrest care

Post-cardiac arrest care aims to optimise survival and neurological recovery by addressing the complex pathophysiology of PCAS [18, 20]. Key priorities include stabilisation of respiratory and circulatory function, neuroprotection, accurate prognostication, and early initiation of rehabilitation [17, 21].

Critical care

Comatose patients with sustained ROSC admitted to an intensive care unit (ICU) after OHCA often present with complex and unstable physiology [22]. Critical care after OHCA involves multimodal strategies aimed at optimising cerebral and systemic oxygenation and perfusion, to minimise secondary brain injury, as illustrated in Figure 1.

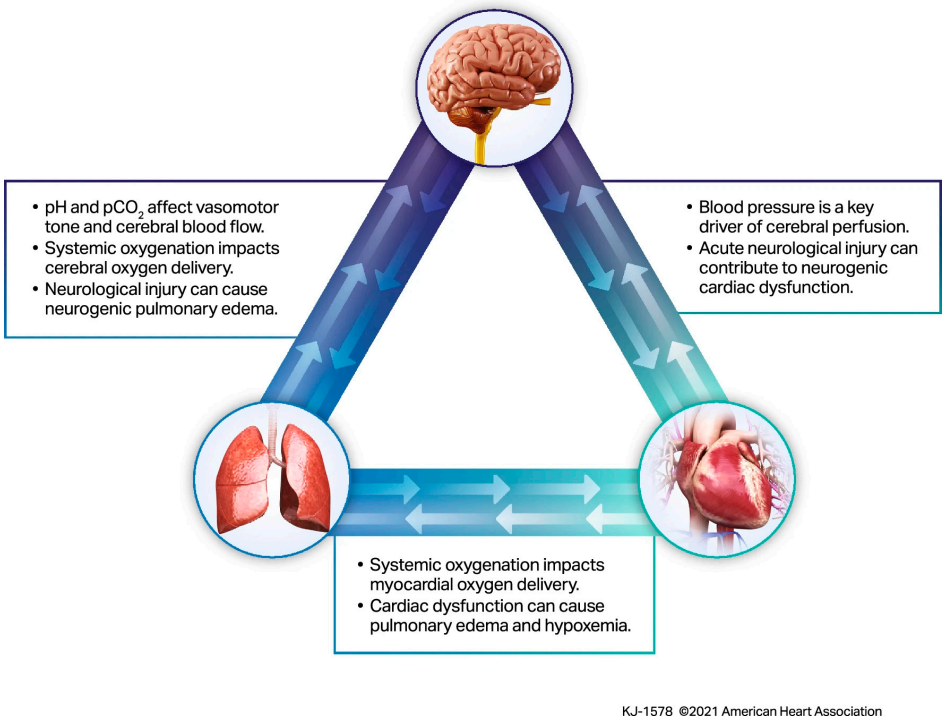

Figure 1 The physiological interplay in neurological, cardiac, and pulmonary systems
This complex interplay necessitates individualised management of the patient in the intensive care unit after cardiac arrest [22]. Reprinted from Neurocrit Care, 40(1), Hirsch KG, et al. Critical Care Management of Patients After Cardiac Arrest: A Scientific Statement from the American Heart Association and Neurocritical Care Society (Fig1), p. 5, https://doi.org/10.1007/s12028-023-01871-6. Copyright The Authors (2023). Reprinted under CC license: BY-NC-ND 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Mechanical ventilation strategies should aim for normoxia and normocapnia [21]. Hemodynamic targets typically include adequate mean arterial pressure and cardiac output to ensure sufficient perfusion of the brain and other vital organs [22], although optimal pressure targets are currently unknown. Figure 2 illustrates ventilation and hemodynamic targets commonly used in the ICU.

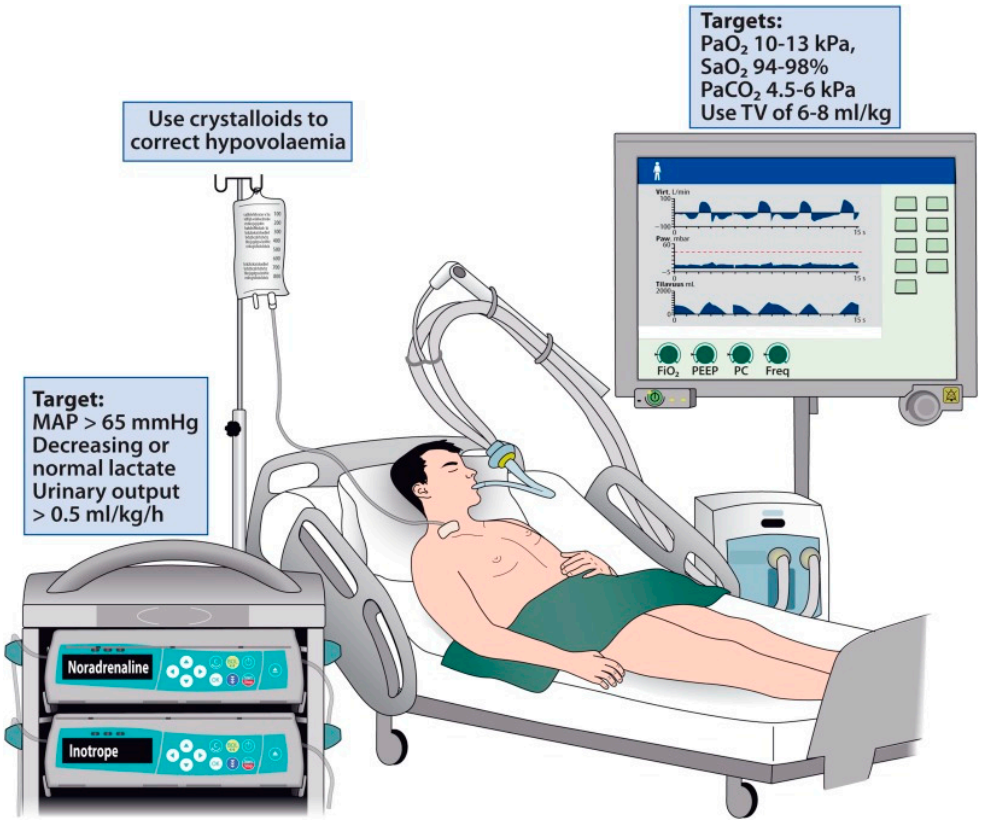

Figure 2 Hemodynamic, oxygenation and ventilation targets

Reprinted from Resuscitation, 161, Nolan JP, et al., European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care, pp. 220-269, Copyright (2021), with permission from Elsevier.

MAP – mean arterial pressure; PaCO2 – arterial partial pressure of carbon dioxide; PaO2 – arterial partial pressure of oxygen; SpO2 – peripheral oxygen saturation; TV – tidal volume.

Neurological monitoring is essential during the acute phase. Continuous electroencephalography (EEG) monitoring can be used for detection and treatment of seizures and status epilepticus—common complications after OHCA that are associated with poor neurological outcome [22, 23].

Critical care after OHCA involves multimodal strategies aimed at optimising cerebral and systemic oxygenation and perfusion, minimising secondary brain injury.

Targeted temperature management

Targeted temperature management has historically been a central intervention in post-cardiac arrest critical care, aimed at reducing neurological injury and improving functional outcomes.

Neither the Target Temperature Management 33 °C versus 36 °C after Out-of-Hospital Cardiac Arrest trial (TTM-trial), nor the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2-trial) could demonstrate any differences in survival or neurological outcomes between temperature interventions in comatose OHCA patients [24, 25]. Several recent systematic reviews and meta-analyses have consistently found no support for the routine use of temperature control in this population [26, 27].

Current evidence does not support the routine use of therapeutic hypothermia

Neurological prognostication

Accurate neurological prognostication after cardiac arrest is essential for guiding decisions on the continuation or withdrawal of life-sustaining treatment (WLST) [17, 28]. While cardiovascular instability or multiorgan failure is the primary cause of death within the first 72 hours after ROSC, severe brain injury accounts for the majority thereafter [28]. Most often this is due to WLST based on an expected poor neurological prognosis.

A multimodal approach for neurological prognosis incorporates clinical examination, electrophysiology (EEG and somatosensory evoked potentials), neuroimaging, and blood biomarkers [18], as illustrated in Figure 3. This multimodal approach reduces the risk of premature WLST [21, 23, 28].

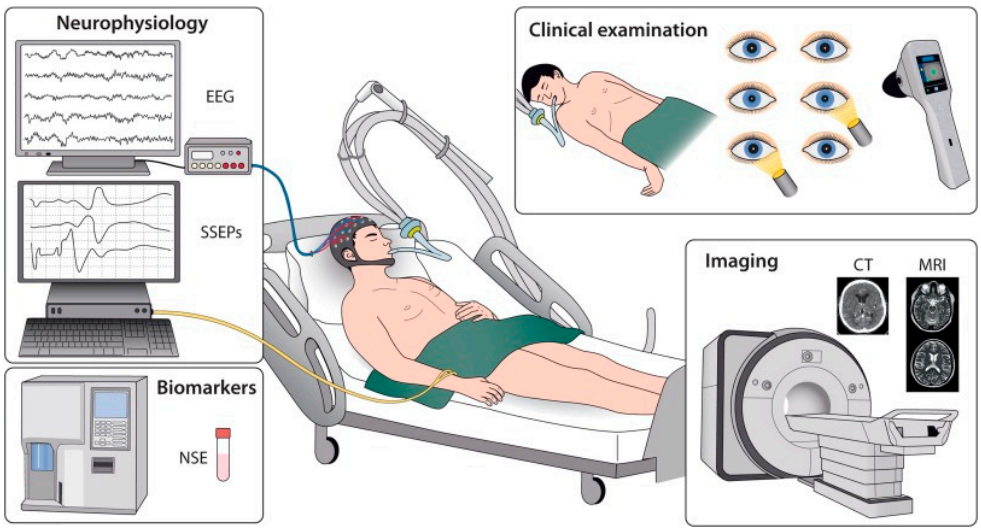

Figure 3 Examples of methods in multimodal neurological prognostication
Reprinted from Resuscitation, 161, Nolan JP, et al., European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care, pp. 220-269, Copyright (2021), with permission from Elsevier.
CT – computed tomography; EEG – electroencephalography; MRI – magnetic resonance imaging; NSE – neuron specific enolase; SSEP – somatosensory evoked potential.

Post-cardiac arrest follow-up and rehabilitation

Structured follow-up and rehabilitation are essential components of post-cardiac arrest care, aimed at addressing the complex challenges commonly experienced by survivors [18, 20, 29, 30].

Cognitive impairments, psychological distress, physical limitations and symptoms of fatigue are common among survivors, which may reduce their quality of life [20, 31-33]. Early cognitive function has been found predictive of functional outcome after hospital discharge, highlighting the importance of screening before hospital discharge [34, 35]. Integrated and parallel pathways with combined cardiac and neurological rehabilitation are particularly encouraged [23, 31, 36]. A Dutch intervention focusing on early follow-up and psychosocial support showed improved quality of life and reduced anxiety for cardiac arrest survivors [37].

Figure 4 illustrates possible rehabilitation and follow-up pathways for cardiac arrest survivors.

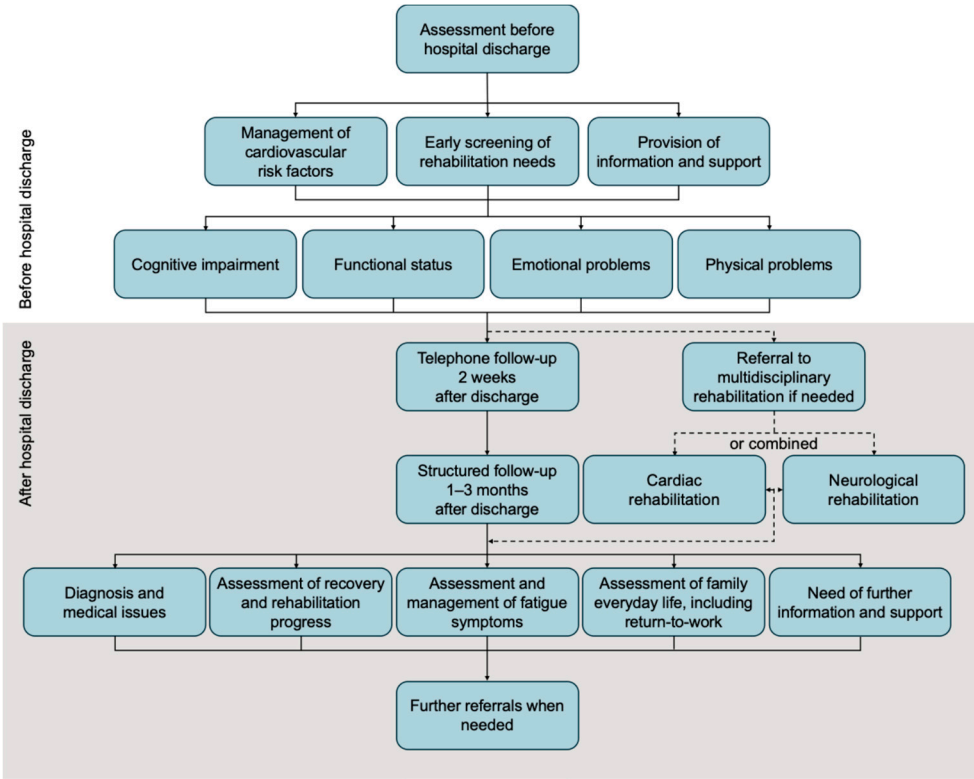

Figure 4 Possible rehabilitation and follow-up pathways for cardiac arrest survivors
Rehabilitation and follow-up pathways for cardiac arrest survivors with early assessments and screening, structured follow-up, with integrated and parallel cardiac and neurological rehabilitation when needed.

Structured follow-up and rehabilitation are essential after OHCA and should address cognitive, emotional, physical, and psychosocial recovery, including functional status and symptoms of fatigue.

Outcomes among OHCA survivors

Key domains of long-term recovery after OHCA include cognitive function, functional status, fatigue, and psychological distress, as these outcomes significantly affect daily life and are linked to HRQoL, influencing survivors' overall long-term well-being.

Cognitive function

The causes of cognitive impairment after OHCA are multifactorial, with hypoxic-ischemic brain injury as a key mechanism, but cardiovascular risk factors may also play a role [38, 39]. Cognitive problems after OHCA are common and although prevalence estimates vary across studies, systematic reviews suggest that around half of all survivors experience cognitive problems [40, 41]. While impairments are generally mild, they can be severe and involve multiple domains [39]. Commonly affected cognitive domains are memory, attention, executive functioning, and processing speed [40, 41]. Particularly impaired memory function has been identified as a significant determinant of poor HRQoL after OHCA [42-44].

Cognitive impairments are common among OHCA survivors and are linked to reduced participation and HRQoL.

Functional status

Although most survivors after OHCA are classified as having a favourable outcome in functional status at hospital discharge [45], outcomes are also influenced by pre-existing comorbidities and socio-economic factors [46]. Recovery of functional status after OHCA is most substantially during the first six months post-arrest [47], with potential improvement continuing up to 18 months [48]. WLST affects the prevalence of severe neurological impairments among OHCA survivors. In countries where WLST is used, few survivors have severe brain injuries [23]. In contrast, where WLST is not practised, more than 50% of survivors have a poor outcome because of hypoxic-ischaemic brain injury [47].

Functional status following OHCA are commonly assessed with a clinician-reported functional outcome measures, such as the modified Rankin Scale (mRS) [49]. In cardiac arrest research, scores often dichotomised into 'good' as favourable or 'poor' as unfavourable [50]. While this reflects functional independence versus dependence, unresponsiveness, or death, it limits its ability to reflect clinically meaningful differences in functional status [46]. The specific classification of mRS is detailed in Table 1.

Table 1. Functional status by the modified Rankin Scale (mRS).

Outcome	Score	Description	Consequences
Good / favourable	0	No symptoms	
	1	No significant disability	Able to carry out all usual activities, despite some symptoms
	2	Slight disability	Able to look after own affairs without assistance, but unable to carry out all previous activities
	3	Moderate disability	Requires some help, but can walk unassisted
Poor / unfavourable	4	Moderately severe disability	Unable to attend to own bodily needs without assistance, or walk unassisted
	5	Severe disability	Requires constant nursing care and attention, bedridden
	6	Dead	

The mRS is commonly used to assess functional outcome after OHCA but has limitations in capturing nuanced recovery when dichotomised.

Fatigue

Fatigue is a complex condition with multidimensional symptoms encompassing physical, cognitive, emotional, and behavioural components [51]. This sense of extreme tiredness and exhaustion is one of the most frequently reported symptoms after cardiac arrest [5], with approximately 70% of OHCA survivors at six months and persistent in nearly half of survivors one year post-arrest [52, 53]. Fatigue is associated with impaired functioning, reduced participation, and poorer HRQoL [54].

Fatigue is common after OHCA and is associated with impaired functioning, reduced participation, and poorer HRQoL.

Psychological distress

Psychological distress, including anxiety and depression, is common after OHCA [18, 55]. Estimated prevalence of anxiety among OHCA survivors is one-fourth (26% [95% confidence interval: 16–39%]) [56], with longitudinal studies suggesting that symptoms can persist over time [57]. Psychological distress is associated with cognitive impairment, fatigue, reduced functional ability, lower societal participation, and increased long-term mortality [58-60].

Psychological distress is associated with cognitive impairment and fatigue, highlighting the interconnected nature of these problems.

Survivors' lived experience

Surviving a cardiac arrest fundamentally alters an individual's identity and life trajectory, as a significant biographical disruption [61]. This disruption can begin upon regaining consciousness, which often can be confusing, accompanied by difficulty adapting to a changed sense of self [62]. The physical, emotional, cognitive, and social challenges that survivors frequently experience, often disrupt their perceptions of 'normality' [63-65]. Despite these challenges, some survivors also report positive changes, including renewed appreciation for life and closer relationships [62]. This emerging sense of coherence and meaning in life forms a foundation for perceived well-being [66].

Survivors participating in rehabilitation programmes, have described it as the first time they felt understood [67]. Rehabilitation that addressed brain injury, psychological distress, and supported the return to daily activities were particularly valuable, and reduced feelings of isolation [65, 67]. Still, many report gaps in discharge planning, lack of information and emotional support as barriers to recovery [68].

Surviving cardiac arrest disrupts identity and normality, with gaps in information and support hindering recovery. Survivorship is a process of regaining self, coherence and well-being.

Patient-reported outcomes

A patient-reported outcome (PRO) is any report that comes directly from an individual about symptoms, functioning, well-being, or HRQoL [69, 70]. *Proxy* assessments, by a close observer, are usually only employed if the person of interest is unable to respond, due to severe illness or cognitive impairment [70]. A patient-reported outcome measure (PROM) is the standardised instrument used to collect these outcomes, offering insights that could reflect the individual's perspective and potentially support patient-centred care [71, 72]. PROMs may be either generic, enabling comparisons across populations and conditions, or condition-specific, focusing on outcomes relevant to a particular group [73].

To accurately capture outcomes that matter to a target population, the importance of a conceptual framework to guide PROM selection is emphasised [74]. A key attribute for a PROM is also a clear measurement model, that specifies the scale structure and scoring methods [75]. While PROMs are increasingly used in research and clinical care to support patient-centred decision-making [76], poor alignment with patient priorities risk limiting the value of PROM use [77].

Selecting PROMs presents a challenge, as each instrument has strengths and limitations depending on its purpose and context [78, 79]. A structured approach to select a PROM includes, defining the concept, identifying existing tools, and evaluate their psychometric properties [80]. The step of evaluating psychometric properties of a PROM in a specific target population or setting is often overlooked.

Health-related quality of life

Health is widely considered a key component of overall well-being or quality of life. The concept of HRQoL was introduced to reflect the impact of health, disease, and treatment on daily functioning and well-being [81]. HRQoL has become a common outcome in health research and clinical trials, emphasising patient-centred perspectives and reflecting a shift toward outcomes that matters to individuals [82].

Conceptual foundations of HRQoL

HRQoL is generally recognised as a multidimensional construct, and a common definition is that it includes individual's perception of how illness or treatment affects the physical, psychological, and social functioning or aspects of their life [83]. A more broadly definition describes HRQoL as those aspects of perceived well-being that are related to or affected by disease, and disability [84]. However, despite the growing recognition of its importance, no consensus on a single definition of HRQoL have been accepted [85, 86].

This has led to varied interpretations, conceptual models, and measurement strategies [81, 87]. In practice, HRQoL is often operationalised through multidimensional instruments that assess domains such as physical, mental or cognitive, and social functioning [82, 83].

There are several conceptual models of how to understand HRQoL. The Wilson and Cleary model links clinical and biological variables to health perceptions and overall quality of life [88]. It was developed to describe pathways through which various factors influence HRQoL. Ferrans et al. (2005) revised the model by clarifying the roles of individual and environmental factors [89]. Individual characteristics include demographic, psychological, and biological factors influencing health outcomes. Environmental characteristics are social and physical influences, such as family, healthcare systems, and living conditions, which can either facilitate or hinder health and quality of life. The model includes five interrelated patient outcomes: 'Biological function'; 'Symptoms'; 'Functional status'; 'General health perceptions'; and 'Overall quality of life'. These domains are connected through dominant causal pathways, illustrated in Figure 5.

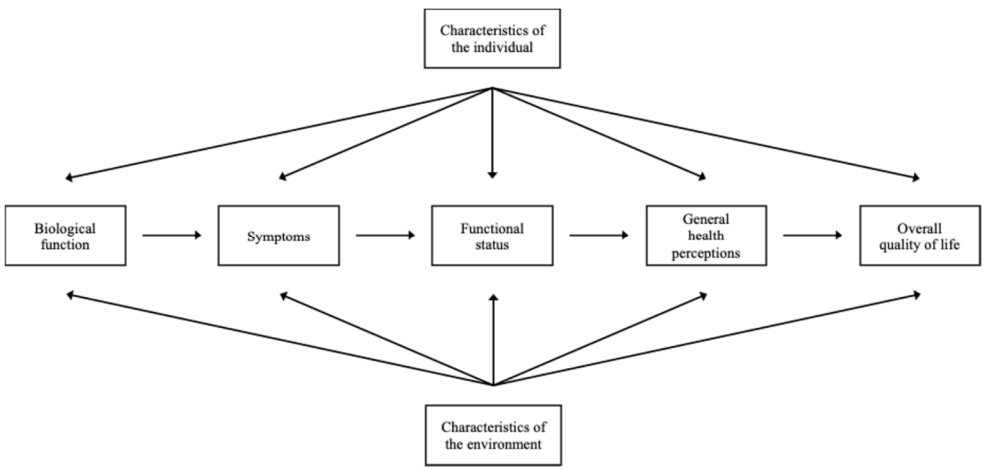

Figure 5 Revised Wilson and Cleary model for health-related quality of life
Adapted from "Linking Clinical Variables with Health-Related Quality of Life: A Conceptual Model of Patient Outcomes," by I.B. Wilson and P.D. Clearly, 1995 [88]. Revised by C. Ferrans et al., Journal of Nursing Scholarship, 2005 [89]. Copyright by *JAMA*. Used with permission.

The International Classification of Functioning, Disability and Health (ICF) provide a framework for describing health, functioning, and disability. The model focus on how health conditions interact with body functions, activities, participation, and personal and environmental factors [90]. Although not a specific model of HRQoL, it is often used to map and compare the content of HRQoL instruments [91]. While these models vary, they commonly link clinical and biological factors, such as symptoms and functional limitations, with perceived health [86].

Health status as distinct from HRQoL

Health status refers to an individual's self-reported physical or mental health, or social functioning and symptoms. It represents a narrower concept than HRQoL, focusing mainly on current health rather than broader well-being [85]. Despite this distinction, HRQoL and health status are often used interchangeably. Instruments described as measures of HRQoL, most often primarily measure health status, and may not meaningfully capture broader aspects of quality of life or subjective well-being [83, 85, 92], and in practice capture what might more accurately could be described as *quality-of-life related health*.

Life satisfaction

Life satisfaction is one of the key components of subjective well-being, reflecting an individual's overall evaluation of their life as a whole [93, 94]. As such, it is not only influenced by objective conditions but also psychological adaptation and personal meaning [95]. Thereby, life satisfaction provides a strong foundation for defining quality of life as a subjective experience determined by how individuals appraise their lives [83].

Unlike health status or HRQoL, life satisfaction is not limited to health-related domains but includes personal values, goals and expectations, and life context [71, 96]. The conceptual differences when comparing these constructs are important as they influence how instruments are interpreted [97].

HRQoL, health status, and life satisfaction reflect different aspects of how individuals perceive their health and lives.

HRQoL, health status and life satisfaction after OHCA

As described, survivors after OHCA often face physical, cognitive, psychological, and social challenges that shape their long-term recovery. For resuscitation to be considered successful, survival alone is not enough—survivors must be able to live with an acceptable quality of life [4, 62, 98], and meaningful recovery requires a broader assessment of survivorship [99]. Thereby, understanding HRQoL, health status, and life satisfaction after OHCA is important.

Methodological heterogeneity

Despite growing recognition of the importance of evaluating HRQoL after OHCA, systematic reviews have consistently identified methodological heterogeneity and lack of consensus regarding its definition, measurement, and reporting [54, 100, 101]. Haydon et al. (2017) concluded that such heterogeneity and inconsistent terminology make survivors' HRQoL after cardiac arrest difficult to evaluate [102]. Similarly, Haywood et al. (2018) found that only a few PROMs had been evaluated in OHCA survivors, often with limited evidence of their psychometric properties [103]. Moreover, most PROMs fail to capture the complexity of recovery or reflect outcomes meaningful to survivors, highlighting the need for a standardised core outcome set with more survivor-centred domains [101, 103, 104]. In the process of forming a core outcome set for cardiac arrest (COSCA), three core outcome domains were included: survival, neurological function, and HRQoL. To capture the survivor perspectives and assess HRQoL, generic PROMs, including instruments such as the EQ-5D-5L and SF-36v2 were recommended [105].

HRQoL in comparison with general population

Cardiac arrest survivors' HRQoL has generally been reported as good, with only small differences compared to general populations [100]. This is supported by several studies showing comparable results with national populations [58, 106-110]. Most often OHCA survivors' HRQoL have only been reported with composite scores [111], with information lacking on detailed health domains; thus, limiting the granularity [112].

HRQoL in relation to demographic and clinical factors

HRQoL one year after cardiac arrest appears to be strongly predicted by demographic factors, early functional status and subjective well-being [44]. HRQoL after OHCA is also influenced by a range of personal and psychosocial factors, including age, neurocognitive recovery, psychological distress, and social support [113, 114].

Biological sex has been highlighted as an important determinant for HRQoL [111], and female survivors experience poorer long-term outcomes and greater psychological distress than males [115-118].

Marital and educational status have also been associated with HRQoL among ICU survivors [119], although their specific influence after OHCA remains less explored [111].

Both comorbidity and clinical frailty have been linked to worse outcomes after cardiac arrest and critical illness [120-123], yet its impact on long-term HRQoL among OHCA survivors remains insufficiently studied.

Life satisfaction in survivors

Survivors' life satisfaction is often reported as comparable to that of the general population [124]. Persistent problems such as pain have been found to reduce survivors' life satisfaction, even without severe health limitations [125]. At the same time, some studies suggest that survivors can remain satisfied with life despite cognitive impairments [126]. This highlights the complex and multifaceted nature of life satisfaction after cardiac arrest. Although a relationship between health status and life satisfaction has been established in cardiovascular diseases [93], this association is largely unexplored in OHCA survivors and remains insufficiently understood.

Association between HRQoL and targeted temperature management

While no consistent association between therapeutic hypothermia and long-term HRQoL have been found, a systematic review concluded that larger trials were needed [127]. More recently, the TTM2-trial reported no significant difference in HRQoL between temperature groups [25]. Previous studies have not accounted for pre-arrest factors—such as age, gender, education level, pre-arrest comorbidity, and marital status, nor have specific health dimensions been explored in detail. Consequently, the long-term impact of temperature management on HRQoL after OHCA remains inconclusive.

Trajectories of recovery

Most improvements in HRQoL and psychological well-being seem to occur during the first 6 to 12 months after OHCA [53, 128, 129]. HRQoL appears stable 6 months after OHCA [48], with similar patterns in both IHCA survivors and ICU survivors [130, 131]. Cross-sectional data also suggest that HRQoL remains stable long-term, even up to 20 years post-arrest [110]. These findings highlight the need for further longitudinal research on how survivors' health status evolves beyond the first year after cardiac arrest.

Co-survivor and caregiver perspective

Beyond the survivor, cardiac arrest also affects family members, or co-survivors [5]. Their experience is often chaotic [132], involving uncertainty, helplessness, and emotional shock [133]. Feelings of constant concern for the survivor and fear of recurrence are also common and may persist over time [134, 135]. The transition home is commonly characterised by family members assuming caregiving roles without sufficient preparation or support, which can lead to emotional, social, and practical changes and feelings of inadequacy and overwhelming responsibility [133-136].

These new responsibilities and shifts in family dynamics, contribute to psychological distress, fatigue, social withdrawal—often exacerbated by lack of information and support after discharge [137]. Caregiving responsibilities and unmet support needs have also been linked to poorer quality of life and negatively affected health [138, 139].

The unmet needs frequently experienced by family members highlight the importance of attention to both survivor and co-survivor perspectives and should be considered an essential component of post-arrest care [61, 136]. The importance of early contact and follow-up from multidisciplinary teams have consistently been highlighted by co-survivors [29, 63, 140].

These challenges underscore the need for structured follow-up, information and psychological support [132, 136, 137]. Similar challenges have been described among caregivers in other ICU populations [141, 142], suggesting that these issues are common across critical illness trajectories. This multidimensional strain experienced by co-survivors is often referred to as caregiver burden and warrants further attention in cardiac arrest care [134].

Family members of cardiac arrest survivors face emotional shock, unmet support needs, and long-term psychological distress, underscoring the need for family-centred post-arrest care.

Caregiver burden

Caregiver burden refers to the perceived negative impact of caregiving on emotional, social, financial, and physical well-being [143]. Although widely recognised as a multidimensional concept, inconsistent definitions and varied measurement tools complicate comparisons across studies [144].

Caregivers of individuals recovering from critical illness may be particularly affected, often needing to adjust their life trajectory and identity. Caregiver burden in this context is influenced by complex interactions between patient and caregiver characteristics [145]. Caregiver burden has been linked to cognitive and functional impairments, particularly when behavioural symptoms are present [139]. Similarly, long-term impairments in survivors after critical illness are associated with higher caregiver burden and worse mental HRQoL [146]. Greater functional dependence, more comorbidities, and being a spouse of the care recipient have all been shown to increase the risk of burden [147, 148], but these associations remain largely unexplored after OHCA.

In OHCA populations, caregiver burden has received some attention. Reported prevalence rates of high burden vary from 0% to 26%, depending on the measurement tool and threshold criteria [48, 139, 149-152]. Interpretation is further hampered by methodological limitations, including small sample sizes and inconsistent use of instruments and thresholds. Although the 22-item Zarit Burden Interview (ZBI-22) has been widely used in caregiving research [153], its application in OHCA contexts remain limited, with detailed description of caregiver burden in this population lacking.

Caregiver burden is linked to cognitive impairment, functional dependence, comorbidity, and cohabitation. Research in OHCA populations remains limited.

Measurement theory

Measurement requires unidimensional interval-level data by definition, where equal differences between values represent equal differences in a single underlying variable with a defined measurement unit [154]. Measurement is central to health outcomes research. In the context of PROM, measurement rather involves systematic observations and estimation of a construct along a continuum, from less to more [155]. A construct refers to a theoretical concept of interest that cannot be observed directly, such as HRQoL [69]. As the construct is unobservable or *latent*, it must first be operationalised through observable item responses as indirect indicators of the latent construct [156]. Measurement theory provides the conceptual and methodological basis for understanding how scores generated by items in an instrument represent the construct intended to be measured [69].

Conceptual framework

The conceptual framework is a defined as a model describing the relationship between the items as indicators and the construct to be measured. A central distinction is whether a construct is operationalised through a reflective or a formative model. In reflective models, the latent construct is assumed to affect responses of the observed indicators, such that these are manifestations of the same underlying construct and are therefore expected to covary [158]. The causal direction flows from construct to indicators. In formative models, the indicators instead define the construct, reversing the causal direction. Changes in the indicators lead to changes in the construct, and correlations among indicators are not required [69].

Rating scales and level of measurement

As most PROMs rely on ordinal rating scales, typically with verbal response options, categories are ranked in order of severity but do not assume equal intervals. Measurement in this context, is achieved by applying defined rules that translate qualitative data such as *'no problems'* to *'extreme problems'*, into numerical values, e.g., 1–5. Summation of item scores is common in PROMs, and rating scale scores are often treated as 'measures' because they result in systematic scores, enabling constructs such as HRQoL to be quantified and compared between individuals and over time. While multi-item instruments enable modelling of the relationship between observed items and the latent construct [69, 157], instruments using cumulative scoring produce total scores that are confined within an artificial range (e.g., 0–100). Figure 6 illustrates how responses to individual items often are assigned numerical values and summed to a total score.

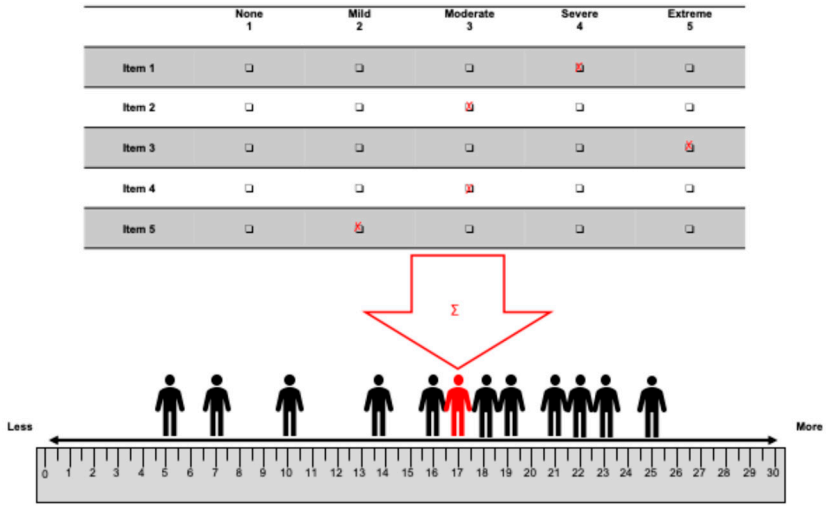

Figure 6 Summation of item responses to a total score
Each response category on a 5-point ordinal scale is assigned a numerical value (1–5), and values across the five items are summed (∑) to produce a total score. Copyright Peter Hagell, Kristianstad University. Modified and reproduced with permission.

Classical test theory

Classical test theory (CTT) is a widely used measurement theory that explains how observed scores can be understood in relation to the construct they are intended to measure. A central assumption within CTT is that the conceptual framework is reflective [158].

In CTT, any observed score is assumed to consist of two components: a true score and measurement error [155]. The true, but unobservable score represents the actual level of the construct for an individual free from measurement error. The true score can be conceptualised as the theoretical average of independent observations, if they could be repeated infinite number of times under identical conditions [159, 160].

Psychometric foundations

To ensure a PROM produces meaningful and interpretable results, its psychometric properties must be evaluated [82]. To support robust evaluation of psychometric properties in PROMs, several frameworks have been proposed, accompanied by standardised terminology to ensure consistency and comparability across studies [160-162]. Transparent reporting of these frameworks and related measurement decisions is essential for rigorous evaluation [163]. Key psychometric properties of an instrument include its validity, reliability, responsiveness, precision, targeting, and interpretability [160].

Validity

Validity refers to the extent to which scores from PROMs truly reflect the construct they are intended to measure [160]. Construct validity is a specific aspect of validity, which evaluates the degree to which the scores of an instrument reflect the construct dimensionality and whether the scores behave as theoretically expected. Construct validity includes structural validity and hypotheses testing, where empirical confirmation provides support for construct validity [157, 161].

Reliability

Reliability refers to the degree to which an instrument yields consistent and reproducible results under stable conditions. It reflects the proportion of observed variance that is due to true differences between individuals, rather than random error [157, 164]. High reliability is essential for distinguishing between individuals or groups and indicates that most of the variance is due to true differences, whereas low reliability indicates that error variance is substantial [159, 160, 162].

Responsiveness

Responsiveness, also referred to as longitudinal validity, is the ability to detect meaningful change in the construct over time [161, 165]. A responsive instrument can not only detect that change has occurred but also accurately reflect the magnitude of that change.

Precision

Precision refers to the degree to which an instrument produces consistent estimates with minimal random error. The standard error of measurement (SEM) is commonly used to quantify precision. A smaller SEM indicates greater measurement precision and implies greater confidence in interpreting individual scores [159].

Targeting

Targeting describes the extent to which a PROM's response categories cover the full range of the construct in the population being measured. Poor targeting may lead to floor or ceiling effects, limiting the instrument's ability to detect differences or change [160].

Interpretability

Interpretability refers to the degree to which one can assign qualitative meaning to a PROM score or a change in score, such as whether a difference is clinically important [75, 166]. It is distinct from other psychometric properties and rather focuses on the contextual understanding of scores.

Rationale

This thesis addresses important knowledge gaps in understanding outcomes after OHCA. Previous research has often relied on broad summary measures, providing limited insight into the specific domains of health and well-being most affected in survivors and their caregivers. Evidence on caregiver burden, long-term recovery, and the measurement properties of PROMs in this population has been sparse, limiting the foundation for clinical follow-up and research. By applying robust psychometric methods, evaluating both survivors and caregivers, and extending the assessment beyond health status to include life satisfaction, this thesis contributes to a more comprehensive understanding of recovery after OHCA.

In addition, conceptual challenges remain. Although HRQoL instruments are widely used, their capacity to differentiate between health status, broader quality of life, and subjective well-being is often unclear. This complicates the interpretation of findings and restricts their utility for both clinical decision-making and research.

Aims of the thesis

General aim

To explore aspects of HRQoL, health status, and caregiver burden among survivors and their informal caregivers after OHCA.

Study specific aims

I. To describe survivors' HRQoL at 6 months in detail, as well as, to investigate possible differences related to sex, age, and population norms.

II. To describe caregiver burden and HRQoL in detail amongst caregivers of OHCA survivors and explore the association with cognitive impairment of survivors. The secondary aim was to compare burden and HRQoL of caregivers to OHCA survivors with caregivers of a matched control group of patients with STEMI.

III. To evaluate psychometric properties of the EQ-5D-5L in OHCA survivors and more specifically: the latent structure of the EQ LSS; age-related differential item functioning (DIF); internal consistency and precision of EQ LSS; and construct validity of EQ-5D-5L.

IV. To contribute to the understanding of longitudinal health status amongst survivors following OHCA. Additional aims were to explore the relationship with temperature management, pre-arrest factors (age, sex, comorbidity, educational level, clinical frailty, and marital status), and life satisfaction.

Study specific hypotheses

II. Caregivers of cognitively impaired OHCA survivors were hypothesised to experience increased burden and decreased HRQoL compared with caregivers to survivors without cognitive impairment.

III. OHCA survivors with more functional dependency and cognitive problems were hypothesised to report significantly more health problems to support construct validity of EQ-5D-5L.

IV. The EQ LSS change score was hypothesised to differ between EQ VAS groups defined by clinically important change. A monotonic negative association with an ordinal anchor (declined, stable, improved) was expected to support responsiveness.

Methods

Overview

An overview of material and methods used in the papers of this thesis is described in Table 2.

Table 2. Overview of material and methods used in the included papers of the thesis.

Paper	I	II	III	IV
Design	Cross-sectional study, post-hoc analysis	Cross-sectional study	Cross-sectional study, post-hoc analysis	Longitudinal study
Study context, ClinicalTrials.gov identifier	The TTM-trial (2010–2013), NCT01020916	The TTM-trial cognitive substudy (2010–2013), NCT01946932	The TTM2-trial (2017–2022), NCT02908308	The TTM2-trial (2017–2022), NCT02908308
Paricipants	442 OHCA survivors	272 OHCA caregivers 108 STEMI caregivers	783 OHCA survivors	836 OHCA survivors
Time-point	6 months	6 months	6 months	6 and 24 months
Main outcome assessment	SF-36v2	SF-36v2 ZBI-22	EQ-5D-5L	EQ-5D-5L
Main statistical analyses	Mann-Whitney U test	Mann-Whitney U test, linear regression	CFA, linear regression, Mann-Whitney U test, Kruskal-Wallis test, Spearman's rho	Linear and ordinal logistic regression, Mann-Whitney U test, Kruskal-Wallis test, ICC, Spearman's rho

Abbreviations: CFA – confirmatory factor analysis; ICC – intraclass correlation; OHCA – Out-of-hospital cardiac arrest; STEMI – ST-segment elevation myocardial infarction; TTM-trial – Targeted temperature management at 33°C versus 36°C after out-of-hospital cardiac arrest trial; TTM2-trial – Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial; ZBI-22 – 22-item Zarit Burden Interview.

Paper I and II

The TTM-trial

The TTM-trial was an international randomised clinical trial (RCT) conducted at 36 ICUs in Europe and Australia between 2010 and 2013. Unconscious (Glasgow Coma Scale <8) adults (age ≥18 years) with >20 minutes of sustained ROSC after an OHCA of a presumed cardiac cause were screened for eligibility of randomisation to a targeted temperature management at either 33 ℃ or 36 ℃ with a 1:1 ratio [24]. Main exclusion criteria were unwitnessed cardiac arrest with asystole as the initial rhythm, >240 minutes between ROSC and screening, suspected or known intracranial bleeding or stroke, hypothermia with a body temperature <30 ℃ [24].

In the trial, 950 patients were randomised and enrolled in the trial, with the modified intention-to-treat sample consisting of 939 patients, used in primary analyses in the main trial. Survivors were invited to participate in a face-to-face follow-up at an institution, or if not possible by telephone at 6 months. Written and informed consent was obtained from participants before follow-up. Of the 491 survivors at 6 months, 455 participated in the follow-up. No difference in all-cause mortality or neurological function at 6 months were found between the two temperature groups [24, 107].

The TTM-trial cognitive substudy

Within the TTM-trial, a cognitive substudy was conducted in Sweden, Denmark, the Netherlands, Italy and the United Kingdom, at 20 of the original 36 sites from the main trial. Patients included in the main TTM-trial at these 20 sites were asked for consent to also take part in the cognitive substudy.

At 6 months after OHCA, survivors were invited to participate in a face-to-face follow-up together with someone that knows them well, defined as a caregiver [167]. In the substudy, patients with STEMI without cardiac arrest were recruited as a control group with an intended ratio of 2:1. The controls were matched for country, age, sex and time-point of hospitalisation (± 2 weeks) [167].

The STEMI control group together with their caregivers completed the same follow-up as the OHCA survivors / caregivers. In the substudy, 287 of 320 (90%) eligible OHCA survivors and 119 STEMI patients participated in the follow-ups.

Cognitive stratification procedure of OHCA survivors

In Paper II, survivors were classified as having either 'no cognitive impairment' or 'cognitive impairment,' based on results from three independent neuropsychological instruments. The full stratification procedure is described in Table 3.

Table 3. Cognitive outcome stratification used in Paper II.

		Categorisation of cognitive outcome	
Instrument	Cognitive domain	No cognitive impairment	Cognitive impairment [d]
FAB [a]	Executive functions	>12	≤12
RBMT [b]	Memory	>16	≤16
SDMT [c]	Processing speed and attention	>–1.5 SD	≤–1.5 SD

Abbreviations: FAB – Frontal Assessment Battery; RBMT – Rivermead Behavioural Memory Test; SD – standard deviation; SDMT – Symbol Digit Modalities Test.

[a] FAB [168] can reliably separate between normal and impaired function [169].

[b] RBMT [170] has robust psychometric properties to detect mild cognitive impairment [171].

[c] SDMT [172], a robust screening instrument [173], was used with age and education adjusted z-score transformation.

[d] Cognitive impairment was defined as a score below pre-defined cut-offs in any of the tests, to indicate at least moderate to severe cognitive problems in at least one cognitive domain. For all tests, lower scores indicates more cognitive problems.

Instruments and outcome measures

SF-36v2

The SF-36v2 was used to assess HRQoL, in both Paper I and II.

The SF-36v2 is a 36-item self-report instrument that measures functional health and well-being across eight domains. Within each health domain, items are recoded so that higher scores reflect better health, then aggregated and transformed to a 0–100 scale, where 0 represents the worst and 100 the best possible health state [174]. To facilitate interpretation, scores were converted using QualityMetric Health Outcomes™ scoring software (version 4.5) into T-scores based on the 2009 U.S. general population norms. The population mean is set to 50 with a standard deviation (SD) of 10. At the group level, deviations greater than three points above or below 50 are generally considered outside the normative range. At the individual level, T-scores <45 indicate impaired functioning in the respective domain [174]. Additionally, one item called Self-Evaluated Transition (SET), is also used to indicate change in health over the preceding year.

From the eight domains, two component summary measures can be derived: the Physical Component Summary (PCS) and the Mental Component Summary (MCS), which capture broader aspects of physical and mental health. Both are calculated as weighted linear combinations of all eight domain scores, with weights derived from factor loadings. Because all domains contribute to both components, positive and negative weights is applied, which subtract variance from the opposite component to prevent double-counting. PCS and MCS are also expressed as T-scores with the same interpretation as the individual domains [174]. The health domains and what they reflect is described in Table 4. How the health domains contribute to the broader component summary measures is illustrated in Figure 7.

Table 4. Description of the health domains of the SF-36v2.

Health domain	Reflects
Physical Component Summary (PCS)	Broader aspect of primarily physical health.
Mental Component Summary (MCS)	Broader aspect of primarily mental health.
Physical Functioning (10 items)	Aspects of physical functioning and limitations
Role-Physical (4 items)	Participation in work or other activities because of physical health problems
Bodily Pain (2 items)	Intensity of pain and the extent of interference with normal work activities
General Health (5 items)	Rating and expectations of general health
Vitality (4 items)	Energy levels, fatigue, and subjective well-bein
Social Functioning (2 items)	Quantity and quality of social activities
Role-Emotional (3 items)	Participation in work or other activities because of emotional health problems
Mental Health (5 items)	Emotional distress, sense of control, and psychological well-being
Self-Evaluated Transition (1 items)	Change in health in general over the last year. Not included in the scoring algorithms.

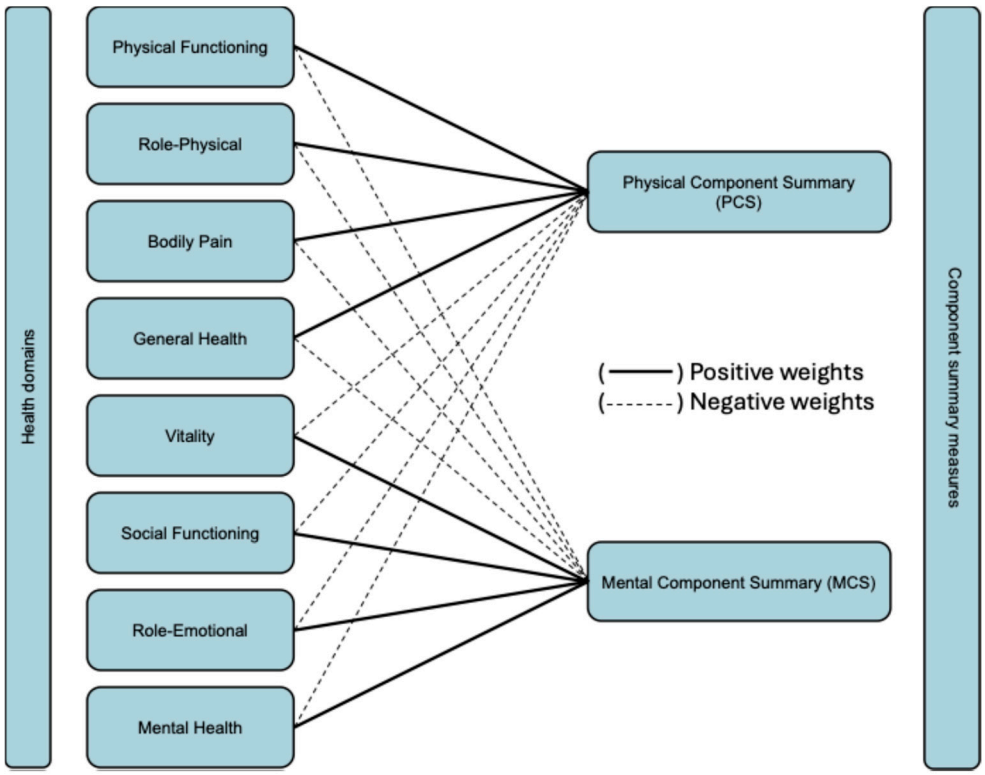

Figure 7 Conceptual illustration of how SF-36v2 health domains contribute to the Physical Component Summary (PCS) and Mental Component Summary (MCS)
Conceptual illustration prepared for this thesis, adapted from SF-36v2 scoring principles.

Caregiver burden

Caregiver burden was assessed by the ZBI-22, which captures different aspects of burden, e.g. feelings of dependency, exhaustion, guilt, embarrassment, frustration, and personal strain [175]. All the 22 items have five ordinal response categories. A total sum score across all items (0–88) can be calculated, with four levels of caregiver burden defined as: no burden (≤20), little to moderate burden (21–40), moderate to severe burden (41–60), severe burden (>60) [176].

Statistical analyses

Descriptive statistics were used to present detailed health domain data of SF-36v2 in both Paper I and II.

Paper I

As the there were no difference in overall HRQoL between the two temperature groups in the TTM-trial [107], all OHCA survivors were treated as one group with no further stratification of temperature intervention.

In Paper I, SF-36v2 was used to describe OHCA survivors' HRQoL as main outcome assessment and was reported with T-scores. It was considered a post-hoc analysis as data analyses were not part of the original study plan and were performed after the initial data collection and analysis. For this thesis, the SF-36v2 domain scores are also reported with 0–100 scores, for comparative reasons.

Psychometric properties of SF-36v2, such as internal consistency, together with floor and ceiling effects were also reported. Subgroup differences, age groups (≤65 or >65 years) and biological sex was analysed with the Mann-Whitney U test. Mean differences in SF-36v2 scores were calculated to indicate clinically relevant differences between subgroups, and with population norms, with Cohen's *d* as indication of effect size (< 0.4 [small]; 0.4–0.8 [moderate]; and > 0.8 [large effect]).

Paper II

As the there were no difference in cognitive function between the two temperature groups in the TTM-trial cognitive substudy [38], all OHCA survivors were treated as one group with no further stratification of temperature intervention.

Associations between ZBI-22 sum score and the SF-36v2 component summaries in OHCA caregivers were analysed with the Pearson correlation coefficient.

Caregiver burden and HRQoL between caregivers of OHCA survivors and STEMI patients were compared with the Mann-Whitney U test (r: < 0.3 [small]; 0.3–0.5 [moderate]; > 0.5 [large effect]).

Associations between caregiver burden and caregiver HRQoL with OHCA survivors' cognitive function were also explored with the Mann-Whitney U test and nested linear regression models. A linear regression model with cognitive function as the only explanatory variable (unadjusted model), was followed by a model including other variables assumed to be associated with caregiver burden and/or HRQoL (as adjusted models). These variables are specified in Table 5.

Table 5. Variables assumed to be associated with caregiver burden and/or HRQoL.

Variable	Definition
Caregiver characteristics	
Age [years]	Age at time of follow-up.
Biological sex	Male/female
Cohabitation status [yes/no]	Living together with OHCA survivor
Survivor related characteristics	
modified Rankin Scale [0–5]	Functional outcome at 6 months after OHCA [49]. Full scale was used.
HADS	Screening tool for symptoms of anxiety and depression [177]. Higher scores indicate more problems with psychological distress.
Anxiety [0–21]	Full scale was used.
Depression [0–21]	Full scale was used.
IQCODE-CA [a]	Observer-reported decline in cognititve function of survivor as compared with before the OHCA.
ICU length of stay [days]	Time from admission to discharge
Hospital length of stay [days]	Time from admission to discharge
Comorbidity index [0–16]	A modified version of Charlson Comorbidity Index indicated pre-arrest comorbidity. Higher scores indicate increased burden of preexisting conditions. Full scale was used.
Country	The country/region in which the participant was included in the trial: Sweden, United Kingdom, Denmark, Italy, or the Netherlands.

Abbreviations: ICU – intensive care unit; IQCODE-CA – Informant Questionnaire on Cognitive Decline in the Elderly - Cardiac Arrest; HADS – Hospital Anxiety and Depression Scale; HRQoL – health-related quality of life; OHCA – out-of-hospital cardiac arrest.

[a] IQCODE-CA scale consists of 26 items each ranging from 1 (much improved) to 5 (much worse) and was calculated by dividing total item sum by the number of items, for a score between 1 and 5; with higher scores indicating greater cognitive decline [178].

Paper III and IV

The TTM2-trial

The TTM2-trial was an international RCT that enrolled adult (≥18 years) unconscious patients after OHCA with a presumed cardiac or unknown cause with sustained ROSC in >20 minutes [179]. To be included in the trial, patients should also be eligible without any restrictions for intensive care. Another criterion for inclusion was ≤180 minutes between ROSC and screening. Main exclusion criteria were unwitnessed cardiac arrest with asystole as the initial rhythm, intracranial bleeding, temperature at hospital admission <30 °C [179].

The trial was conducted at 61 ICUs in Europe, USA, Australia and New Zealand [179]. Patients were randomised to either targeted hypothermia at 33 °C or targeted normothermia and early treatment of fever (≥37.8 °C) in a 1:1 ratio. The TTM2-trial included 1900 patients between 2017 and 2020, with an intention-to-treat population consisting of 1861 patients, of whom 1850 was evaluated for the primary outcome of survival [25].

Survivors were invited to a structured follow-up, at both 6- and 24-months. At 6 months, 836 of 939 (89%) OHCA survivors participated in the follow-up. Proxy reported information was used to assess outcome if survivors were unable to participate in the follow-up [180]. No differences were found between the temperature groups in all-cause mortality, functional outcome (mRS ≥4 defined as a 'poor' outcome), or overall self-reported health by EQ VAS at 6 months [25]. Cognitive impairment was found in 59% of survivors, but no significant difference between the temperature groups [181].

Instruments and outcomes measures

An overview of the PROMs used in Paper III and IV are presented in Table 6.

Table 6. Overview of patient-reported outcomes used in Paper III and IV.

Patient-reported outcomes	Definition
EQ-5D-5L	
Individual dimensions	1 (no problems) to 5 (extreme problems)
Mobility [1–5]	Assess ability to walk
Self-Care [1–5]	Assess ability to wash or dress oneself
Usual Activities [1–5]	Assess ability with e.g., work, study, housework, family or leisure activities
Pain/Discomfort [1–5]	Assess level of pain and/or discomfort
Anxiety/Depression [1–5]	Assess level of anxiety and/or depression
EQ level sum score [5–25]	Summarises scores across all dimensions, where higher scores indicate worse health
EQ VAS [0–100]	A visual analogue scale, where higher scores indicate better overall health
EQ value [0.243–0.976] [a]	Based on general population value sets, where higher scores indicates better health
Life satisfaction (single item) [1–10]	Higher scores indicate better overall satisfaction with life

[a] EQ value was only used in Paper III, where primary analyses were based on Swedish value set **[**182**]** for the whole cohort

EQ-5D-5L

The primary outcome of both Paper III and IV was the EQ-5D-5L. The EQ-5D-5L questionnaire is comprised of a descriptive system with five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression; and a visual analogue scale by EQ VAS [183]. Each dimension has five response levels of severity, scored from 1 (no problems) to 5 (extreme problems), and can either be reported separately or as a descriptive profile with 3125 (55) possible health states. The EQ VAS provides a way to present an individual's perceived current overall health on a visual analogue scale, with the endpoints 0 (the worst imaginable health) and 100 (the best imaginable health). The psychometric properties of EQ-5D-5L have previously never been evaluated in OHCA populations, and it is currently unknown if the use in OHCA survivors is supported.

Another common approach to describe a respondent's health status, is when a descriptive profile is linked to a value set, which provides weights derived from preferences of a general population. This results a single summary index value, the EQ value, or also sometimes referred to as EQ index [184, 185].

Health status can also be presented with the EQ LSS, where scores across all dimensions are summarised [184]. Higher scores on the EQ LSS scale indicate worse health and more limitations. The operationalisation of EQ LSS as a single latent construct of health has been supported when evaluating the scale with item response theory [186].

Life satisfaction

Survivors' perceived life satisfaction was assessed with a single-item question from the World Value Survey: 'All things considered, how satisfied are you with your life as a whole these days?' [187], rated on an ordinal scale from 1 to 10 (completely dissatisfied – completely satisfied).

Other variables and outcome assessments

Variables and outcome assessments used in Paper III and IV.

Pre-arrest variables in relation with health status

Age and biological sex have consistently been associated with HRQoL or health status in OHCA survivors. Comorbidity and education level have also been investigated, but to a lesser extent, and have not yet been significantly associated in multivariable analyses [111]. Although significant associations with clinical frailty and marital status have been found for HRQoL or health status in other similar populations (IHCA) [14], (critical care) [123], (myocardial infarction) [188], it has not yet been explored in a OHCA population. An overview of the variables and how they are defined is presented in Table 7.

Table 7. Overview of independent variables and outcomes assessments used in Paper III and IV.

Independent variables	Definition
Pre-arrest variables	
Age [years]	
Biological sex	male/female
Charleson Comorbidity Index [0–33]	Higher score indicates greater comorbidity
University level education [yes/no]	Any form of university eduction
Clinical frailty scale [1–4 versus 4–9]	Frailty dichotomised as low or high
Marital status [yes/no]	Married or living as married
Status at follow-ups	
Functional status	
modified Rankin Scale [0–5]	0 (no symptoms) to 5 (severe disability). Full scale was used and/or reported.
Cognitive function	
MoCA [0–30]	Used descriptively
Cognitive outcome groups	
No problems [MoCA ≥26]	Dichotomised groups based on established cut-off values, used in hypothesis testing
Problems [MoCA <26]	

Abbreviations: MoCA – Montreal Cognitive Assessment

Cognitive function

Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA), a cognitive performance-based screening tool for mild cognitive impairment, where a score <26 points indicate cognitive problems [189], and support of its validity has been demonstrated in OHCA survivors [190].

Functional status

Functional status was assessed with the mRS-9Q [191, 192], which include 9 questions. It is a clinician reported ordinal scale with 7 levels, from no symptoms (0) to dead (6). Only the first six levels were effectively used as only survivors were included in the analyses.

Statistical analyses

In Paper III and IV, categorical variables and ordinal variables with limited response categories are reported as numbers and percentages. For continuous variables and ordinal variables with ≥10 categories are reported with mean and standard deviation (SD) or median and interquartile range (IQR). A confidence interval (CI) is reported when appropriate. In Paper III, Charlson Comorbidity Index (CCI) [193]; education level; Clinical Frailty Scale (CFS) [194]; and marital status were only used descriptively, whereas they were used as explanatory variables for health status outcome at 6 months in Paper IV.

Paper III

Different statistical methods were employed in the evaluation of psychometric properties of EQ-5D-5L. Latent structure of EQ LSS was evaluated with a confirmatory factor analysis (CFA). DIF for age was evaluated with a baseline model where the latent factor was regressed on age and compared with five separate nested models ($\Delta R^2 < 0.02$ [negligible DIF]; $0.02 \leq \Delta R^2 < 0.13$ [small DIF]; $0.13 \leq \Delta R^2 \leq 0.26$ [moderate DIF]; and $\Delta R^2 > 0.26$ [large DIF effect]). Internal consistency and score precision was evaluated for EQ LSS. Targeting was evaluated with score distribution and floor/ceiling effects. Construct validity of EQ-5D-5L was assessed using hypothesis testing of the mRS and MoCA, with the Kruskal-Wallis test (η^2: < 0.06 [small]; 0.06–0.14 [moderate]; > 0.14 [large effect]), and the Mann-Whitney U test (r: < 0.3 [small]; 0.3–0.5 [moderate]; > 0.5 [large effect]), respectively. Spearman's rho (ρ) correlations were used to assess convergent and discriminant validity.

Paper IV

The associations of EQ-5D-5L at 6 months, with temperature management and the pre-arrest variables were evaluated with linear and ordinal regression models. Due to few respondents with high frailty, the assumptions were not met in the regression models. Consequently, the variable CFS was removed from the analyses. In the revised models, the assumptions were then met.

Respondent's health in each EQ-5D-5L dimension was categorised as improved, declined, or unchanged at 24 months in comparison with 6 months. Change in EQ-5D-5L outcomes between 6 and 24 months for paired samples were evaluated with the sign test. Mean difference of EQ VAS score between 6 and 24 months was used to indicate individual changes over time. Minimal clinically important difference (MCID) was calculated as ± 0.5 SD of the mean difference score. T-test was employed to explore the possible association between change in EQ VAS and temperature management.

To evaluate measurement error, agreement and responsiveness of EQ LSS, a stable subgroup was defined as respondents with EQ VAS difference score within the MCID bands. In this subgroup intraclass correlation (ICC[A,1]), standard error of measurement (SEM), smallest detectable change (SDC) for individuals and group were estimated. Bland–Altman analyses were used to visualise bias and limits of agreement. Responsiveness of EQ LSS was tested across EQ VAS MCID groups with Kruskal-Wallis test (η^2: < 0.06 [small]; 0.06–0.14 [moderate]; > 0.14 [large effect]). The monotonic association with an ordinal anchor (–1, 0, +1) was examined with Spearman's rho (expected order: Declined ≥ Stable ≥ Improved; negative rho). Standardised response mean (SRM) was interpreted as the distribution-based magnitude of change (SRM < 0.2 [trivial]; $0.2 \leq$ SRM ≤ 0.5 [small]; $0.50 \leq$ SRM ≤ 0.8 [moderate]; SRM > 0.8 [large effect]).

Associations between the EQ-5D-5L dimensions and overall life satisfaction at 6 months were explored with Spearman's rho.

Ethical considerations

All studies included in this thesis were based on trials approved by relevant ethical review boards in accordance with national regulations in each participating country. In Sweden, the Regional Ethical Review Board at Lund University reviewed the TTM- and TTM2-trials: Protocol 2009/6 Dnr 2009/324 (TTM-trial); Protocol 2015/8 Dnr 2015/228 (TTM2-trial). To ensure participant safety, interim analyses were conducted by a data safety monitoring board. All procedures complied with the principles outlined in the Declaration of Helsinki [195].

Patients admitted to hospital after OHCA were unconscious at enrolment and therefore unable to provide informed consent at the time of inclusion. Deferred consent procedure was applied, and next of kin were informed as soon as possible. Patients who regained consciousness and the capacity to make a decision, were subsequently asked to provide written informed consent for continued participation. All participants in follow-up studies gave written informed consent and were free to withdraw at any time without stating a reason.

Confidentiality and protection of patient integrity were safeguarded throughout all stages of the research. Data were coded and stored securely, and only authorised research staff had access to sensitive information, and results were presented at group level to ensure anonymity of participants.

Participants did not receive economic compensation, apart from optional reimbursement for travel expenses. Outcome assessors and examiners were instructed to respond with sensitivity to any signs of distress during assessments. If cognitive impairment or emotional problems were identified, and participants consented, referrals were made to primary care or specialist services in line with local clinical practice. These procedures were in accordance with good clinical practice and ensured that participants were not left without appropriate support.

Results

Paper I

At 6 months, 442 of 491 survivors (90%) from the TTM-trial responded to the SF-36v2. Of these were 7% (n = 31) completed by proxy.

Internal consistency was acceptable (Cronbach's $\alpha > 0.70$ for all domains). Ceiling effects were observed for Physical Functioning (15%), Role-Physical (21%), Bodily Pain (44%), Social Functioning (47%), and Role-Emotional (41%).

Mean component summary measure scores (PCS 48.1; MCS 49.9) indicated overall HRQoL within the normative range, whereas Physical Functioning, Role-Physical, and Role-Emotional were all below normative range (Figure 8). Impaired functioning was most pronounced in Role-Physical, where 50% of survivors had a T-score <45.

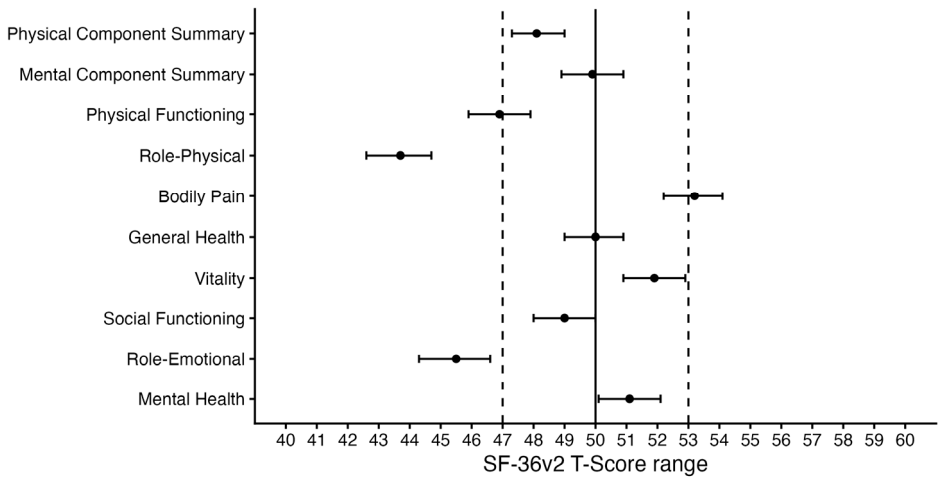

Figure 8 Results of SF-36v2 health domains and component summary measures (n = 440)
Group results for health domains and component summary measures (n = 440). Points indicate mean T-scores with 95% confidence intervals. The solid vertical line marks the 2009 U.S. general population norm (T-score = 50). The dashed lines at 47 and 53 indicate the boundaries for scores considered within the average range.

SF-36v2 domain scores are summarised for T-scores and 0–100 scores in Table 8.

Table 8. SF-36v2 domains presented with both T-scores and 0–100 scores (n = 440).

	SF-36v2 T-scores		SF-36v2 0–100 scores	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Physical Functioning	46.8 (10.8)	51.8 (15.3)	71.9 (28.2)	85.0 (40.0)
Role-Physical	43.6 (11.3)	43.7 (20.2)	62.3 (31.5)	62.5 (56.3)
Bodily Pain	53.2 (9.6)	55.6 (15.3)	78.1 (23.9)	84.0 (38.0)
General Health	49.8 (10.6)	50.8 (15.6)	65.0 (22.2)	67.0 (32.8)
Vitality	51.9 (10.8)	52.6 (11.9)	61.0 (22.6)	62.5 (25.0)
Social Functioning	48.9 (10.4)	52.3 (15.0)	79.1 (25.9)	87.5 (37.5)
Role-Emotional	45.4 (12.6)	49.2 (20.9)	74.2 (30.2)	83.3 (50.0)
Mental Health	51.1 (10.3)	53.5 (14.1)	75.4 (19.6)	80.0 (26.9)

IQR – interquartile range; SD – standard deviation.

Older survivors had poorer Physical Functioning (48.5 vs. 44.1, $p < 0.001$), whereas younger survivors reported worse Vitality (50.8 vs. 53.7, $p = 0.006$) and Mental Health (50.3 vs. 52.6, $p = 0.04$).

The most pronounced difference between male and female survivors was found in Physical Functioning (47.9 versus 41.7, $p < 0.001$, Cohen's $d = 0.6$ [moderate effect size]). The greatest differences between female OHCA survivors and sex-adjusted norm values were found in Role-Physical (40.4 versus 49.3, Cohen's $d = 0.9$ [large effect size]).

In the SET item, 43% of survivors rated their health as somewhat or much worse compared to one year before, while 21% rated it as somewhat or much better. No differences were observed by sex or age group.

Paper II

At 6 months, 287 of 320 eligible OHCA survivors and 119 STEMI patients participated, along with 272 (95%) and 108 (91%) of their caregivers, respectively. Most caregivers were women and cohabiting with the survivor.

Caregiver burden and HRQoL

While overall burden was generally low in OHCA caregivers (median [IQR]: 11 [18]), 28% scored above the cut-off (>20 points ZBI-22). HRQoL was within the norm for both component summaries and domains in SF-36v2.

Burden was negatively correlated with the MCS ($r = –0.49$, $p < 0.001$), but not with the PCS ($r = –0.10$, $p = 0.12$) in OHCA caregivers.

No significant differences in either HRQoL or burden were found between caregivers of OHCA survivors and STEMI patients.

Association of cognitive function with caregiver burden and HRQoL

Caregivers of OHCA survivors with cognitive impairment reported higher burden in ZBI-22 sum [0–88], than those of survivors without impairment (mdn [IQR]: 8.0 [14] versus 18.0 [22], $p < 0.001$, effect size = 0.3 [moderate]), with levels of burden presented in Table 9.

Table 9. Caregiver burden in caregivers of OHCA survivors by cognitive function.

	Cognitive function	
Variable	No cognitive impairment (n = 145)	Cognitive impairement (n = 126)
Level of burden, n (%)		
No burden [≤20]	121 (83)	76 (60)
Little to severe burden [>20]	24 (17)	50 (40)

OHCA – Out-of-hospital cardiac arrest; ZBI-22 – the 22-Item Zarit Burden Interview.

In regression analyses, survivor cognitive impairment was significantly associated with caregiver burden both before (β 7.3 [95% CI: 4.2–10.5]) and after adjustment (β 3.0 [95% CI: 0.02–5.9]). Other significant factors were particularly mRS (β 3.7 [95% CI: 2.0–5.4]); cohabitation with survivor (β 4.8 [95% CI: 1.2–8.4]); modified Charlson Comorbidity Index (mCCI) (β 2.0 [95% CI: 0.4–3.5]), in the adjusted model.

Caregivers of cognitively impaired OHCA survivors reported particularly lower Role-Emotional (mean 45.7 [95% CI: 43.7–47.8] vs. 49.5 [95% CI: 48.0–51.1], $p = 0.002$), compared to caregivers of survivors without cognitive impairment. In regression analyses, survivor cognitive function was not significantly associated with either PCS or MCS.

Paper III

At 6 months, 817 of 939 survivors (87%) responded to the EQ-5D-5L. After excluding two incomplete responses and 32 proxy ratings (3%), 783 participants remained. Dispersion statistics of EQ LSS, EQ value, and EQ VAS are presented in Figure 9.

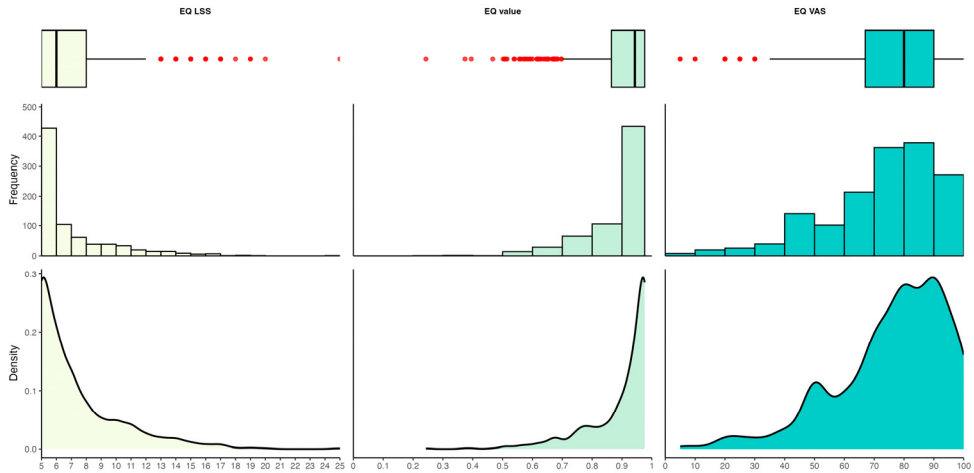

Figure 9 Dispersion statistics
Distribution of EQ-5D-5L outcomes among OHCA survivors at 6 months. Columns show EQ LSS (left), EQ value [based on Swedish value set, range: 0.243–0.976] (middle), and EQ VAS (right). Top row: boxplots display medians, interquartile ranges, and outliers as red dots. Middle row: histograms show observed response frequencies. Bottom row: density plots visualise the smoothed probability distribution.

Latent structure

The CFA showed good model fit, as well as standardised loadings above acceptable threshold, with Self-Care showing strongest loading (0.90) on the latent factor, while Anxiety/Depression the weakest (0.61).

Differential item functioning

DIF related to age was identified for three items: Mobility ($\beta = 0.29$, $p < 0.001$, $\Delta R^2 = 0.019$), Usual Activities ($\beta = -0.07$, $p = 0.044$, $\Delta R^2 < 0.001$), and Anxiety/Depression ($\beta = -0.24$, $p < 0.001$, $\Delta R^2 = 0.017$). All three items had $\Delta R^2 < 0.02$ [negligible].

Internal consistency, precision and targeting

The internal consistency of EQ LSS was consistently high (ordinal $\alpha = 0.88$; ordinal $\omega = 0.81$). The SEM was 1.01 and less than half of the total score's SD (2.9), as expected. Floor and ceiling effects were 35% and <1%, respectively.

Construct validity

In line with hypotheses, survivors with higher functional dependency (mRS) reported more problems across EQ LSS and EQ value (both, $p < 0.001$, $\eta^2 = 0.35$ [large effect sizes]), and EQ VAS ($p < 0.001$, $\eta^2 = 0.18$ [large effect size]). Survivors with cognitive impairment also reported more problems (all $p < 0.001$, $r = 0.15–0.20$ [small effect sizes]).

For convergent validity, strong correlations between EQ LSS and both EQ value [based on the Swedish value set] ($\rho = –0.99$) and EQ VAS ($\rho = –0.59$) were found. Discriminant validity was supported as correlations with life satisfaction were lower ($\rho = –0.50$, 0.51, and 0.58, respectively). Sensitivity analyses when EQ values were based on the UK and French value sets resulted in similar construct validity as the Swedish.

Paper IV

At 6 months, 836 of 939 survivors (89%) participated, and 816 (87%) completed the EQ-5D-5L. At 24 months, 668 survivors (71%) participated in the follow-up, and 663 (71%) completed the EQ-5D-5L. Complete EQ-5D-5L data on both time points were available for 636 (68%).

Ordinal logistic regressions showed no differences between temperature groups in any EQ-5D-5L dimension.

Comorbidity (CCI) was particularly associated with more problems in Mobility, with an odds ratio (OR) of 1.33 [95% CI: 1.18, 1.49], where odds increased 33% per unit of the CCI.

Age in years (OR 0.98 [95% CI: 0.96, 0.99]), biological sex (OR 0.67 [95% CI: 0.47, 0.96]), and marital status (OR 0.65 [95% CI: 0.48, 0.89]) were associated with Anxiety/Depression, with odds of reporting more problems decreased with 2% per year of age, and increased for women and non-married with 49% and 53%, respectively.

Linear regression showed no association between EQ VAS and temperature group. Female sex and not being married were both associated with approximately a 5-point lower EQ VAS score (Figure 10).

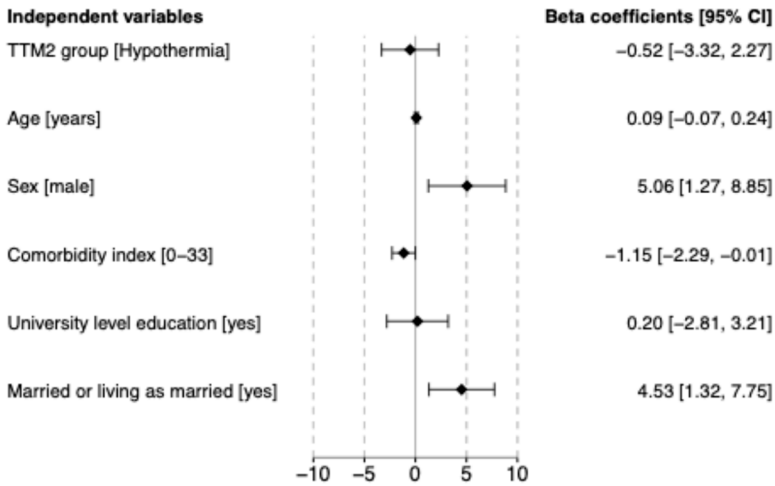

Figure 10 Associations with overall health at 6 month after out-of-hospital cardiac arrest
Forest plot illustrating the associations between EQ VAS [0–100] with temperature management and pre-arrest variables based on linear regression model with participants from the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2) trial (n = 806). Point estimates are presented as unstandardised Beta coefficients with 95% Confidence Intervals (CI). A positive Beta coefficient indicate better overall health. Comorbidity was assessed using the Charlson Comorbidity Index, where a higher score indicates greater comorbidity. Clinical frailty was excluded from the model due to violation of model assumptions.

Change in health status over time

No significant changes were found between 6 and 24 months in EQ-5D-5L dimensions, EQ LSS, or EQ VAS.

Using ± 0.5 SD as the MCID (± 9 points), 27% improved, 26% declined, and 47% had no clinically relevant change in EQ VAS.

No differences between temperature groups were found in EQ VAS difference score (mean difference 0.3 [95% CI: −2.5, 3.0]) (Figure 11).

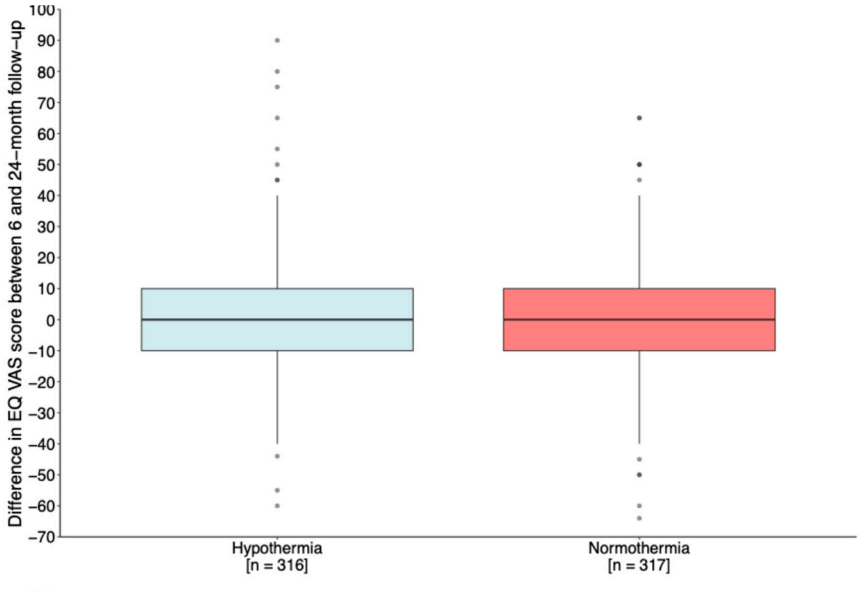

Figure 11 Comparison of EQ VAS differences between temperature groups in the TTM2-trial
EQ VAS [0–100], where higher values indicate better health status, was assessed at 6 and 24 months in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2-trial). The difference in EQ VAS score was calculated for paired samples. Positive values indicate improved health from 6 to 24 months, whereas negative values indicate a decline.

Estimates of measurement error and agreement of EQ LSS change score of the stable subgroup are presented in Table 10.

Table 10. Measurement error and agreement of EQ LSS change score in stable subgroup (n = 296).

Property	Estimates
Intraclass correlation (ICC[A,1]) [a]	0.81 [95% CI: 0.77–0.85]
Standard deviation of within-person differences ($SD_{difference}$)	1.7
Standard error of measurement (SEM) [b]	1.2
Smallest detectable change, individual ($SDC_{individual}$) [c]	3.3
Smallest detectable change, group (SDC_{group}) [d]	0.2
Bland-Altman analyses [e]	bias ≈ −0.1; LoA −3.3 to +3.2

Abbreviations: EQ LSS – EQ level sum score
[a] ICC[A,1] refers to a two-way mixed, absolute-agreement, single ICC.
[b] SEM was calculated as $SD_{difference}/\sqrt{2}$.
[c] $SDC_{individual} = 1.96 \times SD_{difference}$.
[d] $SDC_{group} = SDC_{individual}/\sqrt{n}$.
[e] Bland-Altman bias is the mean within-person EQ LSS differences score, where a value close to 0 indicate small measurement error. Limits of agreement (LoA) are $\pm 1.96 \times SD_{difference}$, and indicate random errror.

When $SDC_{individual}$ threshold for EQ LSS was applied to the full sample, 7% (n = 42) declined, 5% (n = 33) improved, and 88% (n = 561) were within SDC.

EQ LSS change differed across EQ VAS MCID groups (Kruskal–Wallis $\chi^2 = 38.2$, $\eta^2 = 0.06$ [small], $p < 0.001$), with medians ordered Declined ≥ Stable ≥ Improved (Figure 12). EQ LSS change correlated negatively with the ordinal anchor ($\rho = -0.245$ [95% CI: −0.325, −0.163]).

Overall SRM for EQ LSS change was 0.02 [95% CI: −0.05, 0.10]; within anchor group SRMs: Declined 0.33 [0.19, 0.46], Stable −0.03 [−0.14, 0.09], Improved −0.28 [−0.45, −0.13].

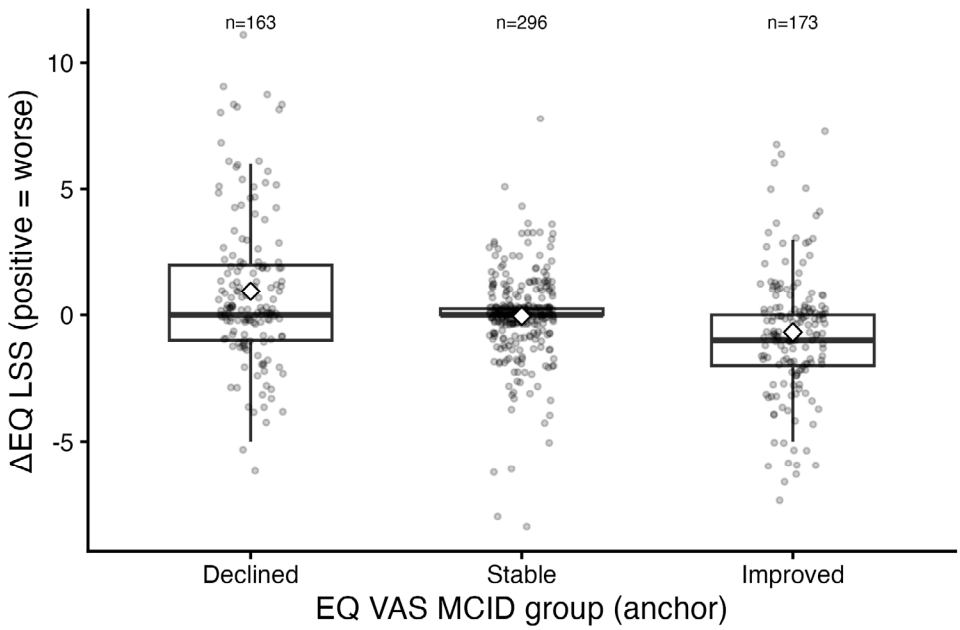

Figure 12 Change in EQ LSS between 6 and 24 months stratified for EQ VAS MCID groups
EQ LSS – EQ level sum score [5–25], higher values indicate more problems. ΔEQ LSS represents the difference in EQ LSS (24-month EQ LSS – 6-month EQ LSS), and positive values indicate more problems at 24 months than at 6 months. Boxes show medians and IQRs; the diamond represents the mean for each group.

Associations between health and life satisfaction

There were moderate negative associations between overall life satisfaction and the individual EQ-5D-5L dimensions at 6 months, with the strongest correlation found for Anxiety/Depression (ρ −0.46 [95% CI: −0.52, −0.41]).

Discussion

This thesis explored HRQoL, health status, and life satisfaction in survivors after OHCA, as well as caregiver burden and HRQoL among caregivers. The thesis also examined the trajectory of health from 6 to 24 months after OHCA.

Across the four studies, the findings generally supported predefined hypotheses and provided a broad understanding of survivor and caregiver outcomes.

The results showed that while many survivors regained health within normative ranges, substantial physical, psychological, and caregiver challenges were observed. This thesis further provides a foundation for how HRQoL and health status among survivors are associated with their cognitive and functional outcome, with age, sex, education, comorbidity, and marital status. The thesis also provides implications for caregiver burden and measurement properties in this population.

Together, this thesis provides new insights into the complex and multifaceted consequences of surviving cardiac arrest, both for survivors and their caregivers.

HRQoL in relation to demographical/clinical variables

Age

In Paper I, the finding of poorer Physical Functioning in older survivors than younger survivors are consistent with previous research [139], although the differences can largely be attributable to advanced age rather than the cardiac arrest itself. The findings that age was inversely associated with Anxiety/Depression (Paper IV) and that younger survivors reported significantly lower Mental Health (Paper I) also align with previous reports after OHCA, where younger survivors showed higher levels of anxiety and depression [109, 196]. In line with this, earlier research has found that older cardiac arrest survivors, when compared with age-matched individuals in the general population, do not report higher levels of anxiety and depression [197]. These findings suggest that advancing age may protect against psychological problems, which can be explained through increased resilience [95, 198], whereas younger survivors remain more vulnerable to impaired mental well-being.

Biological sex

Female survivors were found to have significantly lower HRQoL than male survivors, particularly in Physical Functioning and overall health ratings (Paper I and Paper IV). While this contrasts with some earlier studies reporting no sex differences [199], similar evidence that women experience worse long-term outcomes and greater psychological distress after cardiac arrest has been described both in this and other populations [34, 108, 111, 115, 117, 118]. Possible explanations for these differences include premorbid differences between sexes, as well as biological and clinical factors such as age, comorbidity, and disease severity, rather than sex-specific recovery processes [200].

While the findings are consistent with the general population, comparisons with sex-specific population norms provide more meaningful insights by accounting for premorbid differences in health and well-being. When compared with sex-specific population norms, the negative impact of OHCA on women's health appeared amplified, indicating that the differences represent a true effect and may be further exacerbated by the experience of acute illness [201]. This interpretation was also supported by a multivariable model, including temperature groups, sex, age, education, comorbidity, and marital status, where female sex was independently associated with poorer overall health (Paper IV).

These findings can, at least in part, be explained by that women have poorer cognitive and functional recovery than men [12, 202], both of which are known contributors to reduced HRQoL. Notably, while differences were evident in survivors, no such differences were found among caregivers (Paper II). This contrast suggests that biological sex is more influential in shaping survivors' health outcomes than caregiver burden.

Population norms

At the summary level, most survivors reported SF-36v2 component summary scores (PCS and MCS) that were closely aligned with the general population (Paper I). Similarly, in Paper III, when evaluating EQ-5D-5L, both EQ VAS and EQ values were very close to Swedish population norms when applied across the entire international TTM2-trial cohort.

However, the close alignments with general populations should be interpreted within context. SF-36v2 summary scores may not be granular enough to reflect domain-specific problems [112], or may even distort measurement and score interpretations [203]. That was evident from the substantial impairments in Role-Physical and Role-Emotional, despite normal PCS and MCS values. In addition, SF-36v2 T-scores were based on the 2009 U.S. general population, which may not reflect European and Australian OHCA cohorts, while EQ value results are dependent on the national value set applied.

Furthermore, in Paper III and IV, most survivors reported 'no problems' across each dimension in EQ-5D-5L, including a substantial floor effect that was higher compared with the reference population (35% versus 24%) [204]. Yet, survivors reported more health problems when compared with general population [182], a pattern also described in other OHCA cohorts [108, 205]. This suggests that there is a greater polarisation in OHCA survivors' health status. In contrast, some long-term studies extending five years or longer, suggest that survivors may report outcomes close to the general population [110].

These findings illustrate consistent short-term health problems after OHCA, while long-term research indicate a more heterogeneous picture, which may reflect differences in study design, instruments, and survivor selection.

Functional status

As expected, survivors' functional status was strongly associated with their health status, thereby confirming the study hypothesis in Paper III, with similar findings reported among IHCA survivors [130]. However, a considerable variation was also observed even among survivors with a 'good' functional outcome, a pattern consistent with previous research [114]. This indicates that survivors may experience residual symptoms and psychosocial difficulties despite being functionally independent. While functional status is an important determinant of recovery, this suggests that it does not fully capture the complexity of health after OHCA.

Cognitive function

Cognitive function was associated with both caregiver outcomes and survivor health status, but the effects were smaller and more complex than expected. In Paper II, caregivers of survivors with cognitive impairment reported higher burden in unadjusted analyses, yet this association weakened after adjustment. Similarly, in Paper III, cognitive impairment was significantly associated with health status. While this provided support for construct validity, effect sizes were small. Taken together, this highlight that cognition contributes to survivor and caregiver experiences, but its impact appears to be largely mediated through everyday functioning and dependence.

Comorbidity

Comorbidity emerged as an important factor influencing outcomes in both survivors and caregivers. In Paper II, survivor comorbidity was independently associated with higher caregiver burden.

In Paper IV, comorbidity was independently associated with particularly Mobility, indicating its broad impact on survivors' daily functioning and physical health status. The association between an underlying previous health condition and risk of mobility problems after OHCA, indicate the importance of physical activity both as a primary prevention of cardio-vascular diseases [206], and the targeted rehabilitation need for this group in particular [32, 33]. Taken together, these findings suggest that comorbidity is a key determinant of both survivor and caregiver outcomes after OHCA, consistent with prior evidence showing that it can influence recovery trajectories after cardiac arrest [121, 122].

Marital and cohabitation status

A lack of a partner has previously been identified as a predictor of poorer long-term physical HRQoL after OHCA [44]. Extending on this, marital or cohabitation status, indicating levels of social support, showed consistent but contrasting associations for survivors and caregivers. In Paper IV, marital status was independently associated with survivors' outcomes, with married individuals reporting better overall health and lower odds of Anxiety/Depression. By contrast, in Paper II, caregivers living together with the survivor reported higher levels of burden, which has not been reported for OHCA populations previously. This duality, where cardiac arrest survivors and their spouses influence each other's HRQoL through personality and perceived control, have been shown in dyadic research [207]. While marital status is associated with recovery, psychological well-being, and HRQoL [188], these findings support the view that recovery after OHCA should be understood as a relational process where the well-being of survivors and caregivers is interconnected.

Educational level

University-level education was independently associated with fewer problems in Self-Care. Although the mechanism for this is unclear, higher education may provide resources that support greater independence in daily functioning after OHCA. This association could reflect a broader social determinant such as socioeconomic status seen in the general population [208].

Targeted temperature management

The consistent finding of no differences between temperature intervention groups in Paper IV, either in EQ VAS, EQ LSS, or individual dimensions at six months, or in mean difference of EQ VAS between 6 and 24 months after OHCA, suggest that hypothermia does not affect survivors' health status either in the short or long term after OHCA compared to normothermia.

Life satisfaction

As life satisfaction reflects how individuals evaluate their lives as a whole, it extends beyond health-related domains. This interpretation aligns with the conceptualisation of life satisfaction as a foundation of quality of life [83]. Including life satisfaction in the outcome assessment represents an attempt to move beyond health and to capture dimensions of quality of life that are not visible when using health-focused PROMs alone [209, 210]. Although its relationship with health status remains insufficiently explored in OHCA survivors. Addressing this gap offered valuable insights into survivors' long-term outcomes.

While life satisfaction was included to examine discriminant validity of the EQ-5D-5L in Paper III, it also provided insight into its relationship with survivors' health status. Survivors' life satisfaction appeared broadly comparable to general population levels, and strong associations were observed with different aspects of self-reported health status in EQ-5D-5L. Notably, Anxiety/Depression showed the strongest association with life satisfaction in Paper IV, consistent with findings in cardiovascular populations [93]. This suggest that the EQ-5D-5L may underrepresent the influence of mental well-being compared with physical functioning [211]. However, correlations with overall health measures were stronger than with any single EQ-5D-5L dimension, suggesting that life satisfaction aligns more closely with survivors' general evaluation of their health than with isolated problems in any dimension.

These results support that health status is an important, but not exclusive, determinant of life satisfaction. Broader contextual factors, such as employment, education, and marital status, are also likely to play a role [210], further underscoring the multidimensional nature of recovery after OHCA.

Change over time

Health status among survivors OHCA remained largely stable between 6 and 24 months (Paper IV), with no significant differences observed in either dimensions or overall health in EQ-5D-5L. This aligns with previous studies suggesting that the most pronounced recovery occurs in the first 6–12 months after cardiac arrest [48, 53, 128, 129], with similar trajectories reported for IHCA survivors and ICU survivors [130, 131].

Despite the absence of major shifts in health status between 6 and 24 months, it was evident that considerable individual variation were present. Results in Paper IV, suggested that about one-quarter of survivors declined, one-quarter improved, and nearly half remained stable in EQ VAS.

The stable subgroup analyses indicated a small measurement error over time. When the individual threshold of SDC was applied, only 12% of participants showed change in EQ LSS beyond measurement error, which supports that most survivors were clinically stable. While responsiveness was supported by the anchor-based analyses with a negative monotonic association, only a trivial SRM was found. This indicates that although EQ LSS can capture meaningful shifts in health patients, there is heterogeneous directions of change with possible constraints of floor effects. Therefore, EQ LSS change together with both $SDC_{individual}$, to classify individuals, and SDC_{group} estimates of average shifts should be reported.

In Paper I, more than 40% retrospectively rated their health as worse or much worse over the preceding year on the SF-36v2 SET item. As this question covered both the 6 months before and after the arrest, it may reflect changes directly attributable to the cardiac arrest, whereas EQ VAS captured prospective change between 6 and 24 months, indicating longer-term trajectories. Although conceptually and temporally different, these findings illustrate how perceived change can be captured in different ways.

Caregiver perspectives

The level of caregiver burden observed in Paper II was somewhat higher than previously reported in OHCA populations [48, 150, 151]. A likely explanation was the attempt to include survivors with poorer outcomes, which may have provided a more comprehensive picture of caregiving experiences.

The associations observed between caregiver burden, cognitive impairment, and functional status highlight the interdependence between survivor recovery and caregiver well-being. The finding that functional status emerged as the stronger determinant suggests that it is primarily dependency in daily activities, rather than cognitive impairment in isolation, that drives burden. Cognitive impairment can nevertheless reduce functional status and the ability to perform activities of daily living [212], which are associated with poorer HRQoL and social isolation among caregivers [213]. However, in the regression model, the strong effect of functional status may have reduced the apparent contribution of cognitive function. This could partly reflect multicollinearity, as functional status and cognitive function share much of the same variance, making it difficult to separate their independent effects.

Comorbidity and cohabitation, in addition to functional dependency, were also independently associated with caregiver burden, aligning with findings in systematic reviews after critical illness [147]. These results underscore that underlying health problems and social context can affect long-term caregiver burden independent of cardiac arrest-specific factors.

Despite including a broad set of survivor- and caregiver-related factors, the adjusted regression model explained about one-third of the variance in caregiver burden. This highlights the complexity and individual nature of caregiving, which is also shaped by contextual factors such as coping abilities, role expectations, and social support [148, 214]. Being married further illustrates this duality, while it appeared beneficial for survivors' health and emotional well-being, cohabitation simultaneously added strain for caregivers. Social support has been proposed as mediating factor, possibly reducing the negative effects of survivor dependency on caregiver well-being [212], which highlights the importance of assessing social support networks [215].

Psychometric properties

Psychometric properties of both SF-36v2 (Paper I) and EQ-5D-5L (Papers III–IV) were evaluated for assessing outcomes in OHCA survivors. Together, the findings provide insights into the strengths and limitations of these widely used generic instruments in this population.

Internal consistency was acceptable for all SF-36v2 domains and for the EQ LSS, indicating that items within each scale were sufficiently interrelated. Measurement error analyses (Paper IV) showed that EQ LSS had satisfactory agreement over time, providing estimates useful for detecting change at individual and group level.

Ceiling effects were evident in several SF-36v2 domains, particularly Role-Physical, Role-Emotional, Social Functioning, and Bodily Pain—suggesting limited sensitivity to further improvements in high-functioning survivors. Conversely, there was a similar floor effect in the EQ LSS, with over one-third reported no problems across all dimensions, albeit smaller than previously shown in this population for EQ-5D-3L (46%) [216].

The hypothesised unidimensional structure of EQ LSS was supported in Paper III. That the CFA indicated good fit and all items contributed to the latent construct of health status, was comparable to a cohort of patients with heart failure [217]. Support for construct validity was also indicated through known-groups discrimination, where survivors with functional dependency or cognitive impairment consistently reported worse health, in line with previous findings [218, 219].

While DIF analyses identified statistically significant but negligible age-related effects in three EQ-5D-5L dimensions, it suggests that responses largely reflected survivors' overall health status rather than systematic age bias [220].

Overall, both SF-36v2 and EQ-5D-5L demonstrated acceptable psychometric properties in this population. However, the observed floor and ceiling effects highlight the limitations of generic PROMs in capturing subtle problems in OHCA survivors, especially among those with good recovery. They remain useful for broad population-level assessments but may lack the sensitivity needed to capture nuanced improvements. This empirical evaluation of psychometric properties from large international OHCA cohorts addressed the knowledge gap identified in previous systematic reviews and indicated support for the use of these PROMs in this population [103].

Methodological considerations

A key strength of the studies included in the thesis is that they used data from two large, international RCTs, which provided high-quality outcome data with rigorous follow-up procedures. Through structured follow-up protocols, including telephone assessments, standardised manuals, training of assessors, and central monitoring, missing data were minimised. These strategies enabled data collection from survivors with adverse outcomes.

Despite these strengths, there are several methodological issues that needs to be addressed.

Study design and analytic approach

Non-parametric methods were applied where possible to account for the ordinal nature and skewed distribution of the data, reducing the risk of inappropriate conclusions. Parametric methods were used only after consultation with a statistician to ensure assumptions were met. While this strengthened the robustness of results, no adjustments for multiple testing were made due to the exploratory nature of many analyses, increasing the risk of type I error. Marginally significant p-values should therefore be interpreted with caution. Where appropriate, 95% CIs and effect size estimates were also reported.

Multivariable analyses

In Paper I, analyses of HRQoL were limited to univariable and descriptive comparisons. The absence of multivariable analyses reduces the ability to account for confounding factors, thereby limiting interpretability of associations. Paper II and IV addressed this limitation by applying adjusted regression models.

Skewed samples

There was a clear imbalance in biological sex in the included studies. In Paper I, III, and IV around 82-85% of participants were male. While these imbalances were greater than reported in OHCA epidemiology research (57–72%) [221], comparable outcome studies after OHCA report similar proportions (64–94%) [111]. Poorer outcome among females, both in terms of survival rates and neurological outcome can explain some of this difference [12]. In Paper II there was an inverse relationship, with 83% of the caregivers being females, highlighting the duality between survivorship and co-survivorship, in which men are more often survivors and women more often co-survivors.

Although most OHCA survivors achieved a level of HRQoL comparable to the general population, these results primarily reflect survivors with favourable neurological recovery. To increase granularity of mRS, the full scale was used, in line with guidelines [105, 222]. While no clear evidence of systematic attrition bias was observed, it cannot be fully excluded. Survivors with the most severe impairments may still have been underrepresented, a limitation commonly noted in outcome research after cardiac arrest and other critical illnesses [102, 223, 224].

Assessment of cognitive function and outcome categorisation

Two different approaches were used to dichotomise cognitive outcomes. In Paper II, categorisation was based on identifying at least moderate to severe cognitive problems in one or more domains using three separate instruments. This approach was chosen to reduce the number of statistical comparisons and to ensure that the groups reflected meaningful differences in cognitive function, thereby limiting false-positive findings [225]. While this facilitated interpretation, it has not been validated and remains a limitation, as misclassification cannot be excluded. In Papers III and IV, MoCA was used to indicate cognitive function based on established thresholds. Although the use of MoCA in OHCA populations is supported, more refined classifications that combine MoCA with Symbol Digit Modalities Test (SDMT), may provide greater accuracy [226].

Use of proxy

The role of proxies varied across the studies. In Paper I and Paper IV, proxy reports were included to enable participation of survivors with more severe impairments and reduce attrition bias. This decision supported inclusivity but introduces uncertainty, as proxies may either overestimate or underestimate subjective experiences such as HRQoL [227]. In contrast, proxies were excluded in Paper III, where the psychometric properties of EQ-5D-5L were evaluated, to avoid introducing additional measurement error. This trade-off illustrates the attempt of both maximising representativeness and ensuring measurement validity.

Conceptual and measurement considerations

As previously described, PROM scores are shaped by their operationalisation, that is, how constructs are translated into items, response options, and scoring rules [156]. The rationale for applying EQ LSS was to evaluate its potential as an outcome measure in OHCA research, given prior support for its scalability and practical use [186]. Although the EQ-5D-5L was not designed as a fully reflective scale, the hypothesis that EQ LSS reflects an underlying health construct was empirically tested using a CFA for ordinal data. In Paper III, this analysis supported a unidimensional latent structure. However, other studies have suggested more complex structures [228], underscoring the need for clear conceptual foundations and for distinguishing between reflective and formative indicators [84].

A limitation of sum scores is that assigning values to ordered categories does not create interval-level data, as gaps between categories may not represent equal differences [154]. Treating ordinal scores as interval-level can lead to biased effect sizes, misleading correlations, and inappropriate use of parametric tests [229, 230]. With cumulative scoring, the artificial range of the scale also means that small changes in total score at the extremes may mask large changes in the construct, thereby reducing discrimination and increasing error [231].

In Paper III and IV, SEM was used to evaluate measurement error, but as it is constant across the scale it may underestimate error at the floor and ceiling [232]. While summation of EQ-5D-5L items was supported in Paper III and applied in Paper IV, true interval-level measurement without constraints at the extremes of a scale cannot be established within the limits of CTT. Another limitation of CTT is that an individual's score depends on the scale and sample rather than being an independent estimate of the construct [232]. Achieving true interval-level measurement requires modern psychometric methods, such as Rasch modelling, which provide invariant, interval-level estimates along a construct's continuum [232].

Moreover, although EQ LSS avoids bias from population-based weights, its construction is not assumption-free. In particular, it assumes that each item contributes equally to the underlying construct, an assumption that may not fully hold in OHCA survivors. More generally, the clinical meaning of PROM scores remains difficult to interpret, not only for EQ LSS but for PROMs in general [74, 166, 233]. As their meaning depends on clearly defined scoring and interpretation rules [155], both statistical and qualitative evaluations are needed to ensure clinical utility [234].

These issues highlight the importance of conceptual clarity, whether HRQoL instruments truly reflect individual perspectives, due to their predefined domains, reliance on generic population weighs, and restrictive response formats, which may not capture meaningful outcomes for an individual [235].

Assessment of life satisfaction with a single item

Life satisfaction was assessed using a single-item measure in Papers III and IV. Single items have advantages in terms of brevity and reduced respondent burden, especially when cognitive problems are present. However, they limit reliability and nuance compared to multi-item scales, and the interpretation of the score is ambiguous since it excludes detailed description of life satisfaction experienced by the survivors. For complex constructs, multi-item instruments are generally recommended [69]. The moderate correlation between EQ-5D-5L and life satisfaction suggests that while health status contributes to overall life evaluation, it does not fully account for it. This aligns with previous findings that individuals with significant health problems may still report high quality of life [83]. While the analyses were not designed to fully establish life satisfaction in a conceptual role or to determine causal direction, the single-item measure added an important perspective. This choice reflects the trade-off between feasibility and conceptual precision.

Evaluation of psychometric properties

For SF-36v2, only a limited psychometric evaluation was performed, suggesting that its use in OHCA survivors should be evaluated further.

Although the ZBI-22 was evaluated in detail on item-level, the psychometric properties were not evaluated, limiting confidence in the robustness of the conclusions that can be drawn from those findings.

Change over time and responsiveness

While the approach to evaluate measurement error, agreement, and responsiveness of EQ LSS in Paper IV was pragmatic, several considerations warrant discussion.

Although responsiveness of EQ LSS was supported, with change scores aligning with clinically meaningful EQ VAS groups, the trivial effect size indicates that this result should be interpreted with caution. Using EQ VAS as an anchor for defining stability was clinically meaningful, but as a single-item measure it may not fully capture health status and is prone to fluctuations. Defining stability by the MCID of ± 0.5 SD is supported [236], though alternative anchor- or distribution-based methods could have provided stronger evidence.

Estimating ICC, SEM, and SDC in the stable subgroup followed guidelines [237] and yielded interpretable results, but the long interval between 6 and 24 months may have allowed true clinical changes to occur, complicating the interpretation of stability.

Moreover, the categorisation of change in health as ‘improved’, ’stable’, or ‘declined’ facilitated interpretation but possibly grouped heterogeneous trajectories together. For example, a small decline in a high-functioning individual was treated the same as a larger decline in a more impaired survivor, potentially obscuring clinically meaningful patterns. The categorisation also introduced arbitrary thresholds that may not reflect survivors’ subjective experiences of change. More refined approaches, such as individualised anchors could have provided more nuanced insights.

HRQoL is influenced not only by an individual’s perceived health status but also by how they interpret and adapt to their condition over time [89]. Survivors may recalibrate internal standards or expectations, leading to underestimation of change—a phenomenon known as response shift [238]. Such shifts are especially relevant in populations with chronic illness or acquired disability, which may partly explain why survivors report stable or improved HRQoL despite persisting symptoms. The lack of assessment of internal appraisal therefore represents a limitation of Paper IV. As EQ-5D-5L focuses mainly on functional limitations, it may be less susceptible to response shift, but this also means well-being could have been underestimated.

Small fluctuations in self-reported health are also common in the general population and may partly explain the minor changes observed in Paper IV. However, group-level stability does not imply that no meaningful change occurred, and not every observed change is clinically important [239]. To establish clinical significance, the threshold for detecting change must exceed the threshold for clinically important change [240], underscoring both the importance and the limitations of the SDC and MCID approaches applied in Paper IV.

Conclusions

General conclusions

This thesis set out to deepen the understanding of different aspects of outcomes after OHCA by examining HRQoL, health status, life satisfaction and caregiver burden. By combining detailed analyses of patient- and caregiver-reported outcomes with psychometric evaluation of widely used instruments, it contributes to a more nuanced picture of recovery in this population.

The findings suggest that OHCA survivors generally maintain their health status long-term. For the minority who experience deterioration, the challenge lies in early identification. Screening for factors such as social support, functional limitations, and psychological symptoms may help to target those at greatest risk of poor outcomes. Longitudinal monitoring therefore remains important, both to identify vulnerable individuals and to evaluate interventions aimed at improving long-term recovery.

This thesis also adds to the limited evidence base on caregiver outcomes. Caregiver burden was found to be linked to cognitive impairment, functional dependency and comorbidity in survivors, which was amplified in cohabiting relationships. Importantly, severe burden was uncommon, but even moderate levels can affect emotional well-being and HRQoL. These findings emphasise that incomplete recovery in survivors can have consequences for caregiver well-being, underscoring the need for integrated approaches that address both patient and caregiver needs throughout recovery.

At the measurement level, this thesis contributes by demonstrating acceptable psychometric properties of SF-36v2 and EQ-5D-5L in OHCA survivors, while also highlighting their limitations. Floor and ceiling effects were common, limiting the instruments' sensitivity to detect subtle problems or improvements in survivors. Responsiveness of EQ-5D-5L was modest, reflecting measurement constraints. These findings confirm that generic PROMs may not fully capture the complexity of recovery after OHCA and calls for more conceptually robust and survivor-centred approaches.

Importantly, this thesis also extended outcome assessment beyond health status by including life satisfaction. Although assessed with a single item, life satisfaction provided a valuable complement to health-focused PROMs, revealing associations with mental health and pointing towards broader contextual influences such as social support. This reflects the multidimensional nature of recovery and resonates with theoretical perspectives framing life satisfaction as a foundation of quality of life.

Taken together, these studies highlight that while many OHCA survivors achieve favourable recovery, meaningful impairments persist for a substantial minority, with consequences for both survivors and their caregivers. By evaluating the psychometric properties of generic PROMs, reporting the sustained impact on caregivers, and extending outcome assessment beyond health status with life satisfaction, this thesis helps fill important knowledge gaps. It strengthens the empirical foundation for PROM use in OHCA research and clinical follow-up, while pointing to the need for more sensitive and integrated approaches to long-term outcome assessment.

Clinical implications

The results of this thesis have several implications for clinical care and long-term follow-up after OHCA. Survivors who have favourable neurological recovery at six months generally maintain their long-term health status. However, a substantial minority do experience deterioration, highlighting the need for early screening for risk factors such as functional limitations, comorbidity, social isolation, and psychological distress to identify those most vulnerable to poor outcomes. Survivors identified as at risk should be monitored longitudinally and offered tailored rehabilitation or psychosocial support.

Second, caregiver well-being must be recognised as an integral part of post-arrest care. Caregiver burden was primarily linked to survivor dependency and comorbidity and was amplified in cohabiting relationships. Even though severe burden was uncommon, emotional strain and reduced role functioning were evident. Clinicians should therefore acknowledge caregiver needs alongside patient outcomes and provide information to support recovery. Integrating caregivers into care planning may help to strengthen both survivor recovery and caregiver well-being.

Third, the evaluation of psychometric properties in this thesis shows that widely used generic PROMs are acceptable for broad assessment in OHCA survivors but have notable limitations, including floor and ceiling effects and modest responsiveness. These shortcomings restrict their sensitivity in detecting subtle or residual problems in highly recovered survivors. Clinicians and researchers should be cautious when interpreting scores and recognise that stability in PROMs does not always indicate absence of change.

Finally, the inclusion of life satisfaction in this thesis highlights the importance of extending assessment beyond health status. Life satisfaction reflects survivors' overall evaluation of life and captures dimensions of recovery not fully represented in health-focused PROMs, particularly those linked to mental health and social context. Its integration into outcome assessment may provide a more comprehensive understanding of recovery trajectories and guide patient-centred care.

Future perspectives

This thesis highlights several areas that warrant further investigation:

More longitudinal research is needed on co-survivor outcomes to clarify how caregiver burden evolves over time after OHCA, and to identify protective factors such as coping strategies or social support structures. Moreover, the association between burden and life satisfaction should be explored among OHCA co-survivors. The psychometric properties of instruments used to assess caregiver burden should also be evaluated in a OHCA population.

To investigate possible response shifts, longitudinal qualitative or mixed-methods approaches should be used to better interpret change in PROM scores. Qualitative research may provide insight into how survivors understand and give meaning to reported health problems, and how these translate into clinical consequences.

Future research should aim to develop models of recovery after OHCA that include several different outcomes. Structural equation modelling may be useful to study how cognitive and functional outcomes, symptoms of psychological distress, and fatigue are related to each other and to health-related quality of life.

Future studies should also investigate the causal pathways linking health, psychological adjustment, social context, and life satisfaction, and how these factors influence recovery. In addition, structured multidisciplinary follow-up interventions should be tested. These should include both survivors and caregivers, and be evaluated in terms of health, caregiver burden, and well-being.

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Health-related quality of life after out-of-hospital cardiac arrest

This thesis shows that while many survivors of out-of-hospital cardiac arrest (OHCA) report health-related quality of life (HRQoL) comparable to the general population, their self-reported health remains largely stable between 6 and 24 months, yet a substantial proportion experience limitations in role functioning. By highlighting the impact on caregivers—particularly when survivors live with lasting functional dependence or cognitive impairments—and by evaluating generic patient-reported outcome measures (PROMs), this work addresses key knowledge gaps and strengthens the evidence base for more integrated and sensitive approaches to long-term outcome assessment.

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