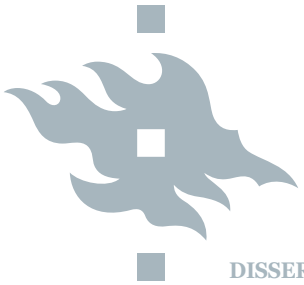

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ILMAR EFENDIJEV

Cardiac Arrest Patients in Finnish Intensive Care Units: Insights into Incidence, Long-Term Outcomes and Costs

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INTENSIVE CARE AND PAIN MEDICINE
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CARDIAC ARREST PATIENTS IN FINNISH INTENSIVE CARE UNITS: INSIGHTS INTO INCIDENCE, LONG-TERM OUTCOMES AND COSTS

Ilmar Efendijev

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Lecture Hall 3, Helsinki Biomedicum, Haartmaninkatu 8, on 1 March 2019, at 12 noon.

Helsinki, 2019

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To my dear Venluska

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Vantaa, Finland
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CONTENTS

ABSTRACT

Background: Sudden cardiac arrest (CA) represents a significant cause of death worldwide. Post-CA mortality remains high, although a steady decline in mortality rates has occurred since the implementation of the 'chain of survival'. This concept refers to a specific and properly timed series of actions directed towards improving post-CA outcomes. In-hospital patients carry a particularly high risk of CA, both on the general ward and in the intensive care unit (ICU). With over 10,000 CAs occurring daily globally, undoubtedly CA has a significant socioeconomic impact. However, data on in-hospital CA (IHCA) and CA-related healthcare costs in Finland, as well as globally, remain limited. Critically ill patients are often admitted to ICUs to undergo complex treatments that may or may not influence patient outcomes. Yet, changes in treatment intensity can potentially reflect a specific patient's clinical condition and carry additional prognostic value.

Aims: This study aimed to systematically review published literature on in-ICU CA (ICU-CA), to investigate outcomes and healthcare-associated costs for CA patients treated within Finnish ICUs and to explore the individual effects of early treatment intensity and cardiopulmonary resuscitation on hospital mortality amongst Finnish ICU patients.

Methods: This study consisted of a systematic review of the published literature (study I) summarising scientific evidence on CA in critically ill patients, and three original substudies on patients treated in Finnish ICUs between 2003 and 2013. The data for the substudies were acquired from the databases of the Finnish Intensive Care Consortium (FICC), the Social Insurance Institution of Finland (SII) and the Finnish Population Register Centre. Two of the substudies included patients from all Finnish ICUs, whilst one substudy consisted of patients from a single tertiary teaching hospital. Study endpoints were ICU-CA incidence and hospital mortality (study II), the association of treatment intensity and hospital mortality (study III) and survival and neurological outcome at one year after CA (study IV). Cost data comprised index hospitalisation expenses, rehabilitation costs and social security costs up to one year after CA. Effective cost per one-year survivor reflected the economic impact of CA, calculated as the sum of the total of healthcare costs divided by the number of survivors.

Results: Across substudies, patient population size varied from n = 1024 to n = 164,255. A systematic review of the literature analysed 18 studies published between 1990 and 2013. Most of the reviewed publications were single-centre and retrospective. Incidence and the outcome of ICU-CA in the published literature varied widely depending upon the study population and settings. In Finland, there were 29 ICU-CAs for every 1000 ICU admissions. ICU-CA hospital mortality reached 56%. Amongst CA patients treated in a tertiary teaching hospital ICUs, 58% of out-of-hospital CA (OHCA) patients, 41% of IHCA patients and 39% of ICU-CA patients remained alive at one year following the initial arrest.

Amongst all one-year survivors, 88% to 94% had a favourable neurological outcome. The effective cost, expressed in 2013 euro, was €94,688 for a one-year survivor and €102,722 for a one-year survivor with a favourable neurological outcome. A CA event and poor preadmission functional status, defined as full dependency in self-care, were associated with a similar increase in the risk of hospital mortality. An increase in the intensity of early treatment associated with a higher risk of in-hospital death, particularly amongst patients with an initially low mortality risk.

Conclusions: The incidence of ICU-CA amongst Finnish critically ill patients was higher and mortality was lower than previously published findings. Amongst ICU-treated CA patients, the effective costs for one-year survivors were comparable to or lower than costs for ICU-treated patients with acute renal failure and critically ill cancer patients, healthcare expenditures considered generally acceptable. The increase in the risk of in-hospital death due to CA was comparable in magnitude to a poor preadmission functional status. Early increase in treatment intensity can serve as an additional warning sign of deterioration in Finnish critically ill patients.

TIIVISTELMÄ

Äkillinen sydämenpysähdys on merkittävä kuolinsyy maailmanlaajuisesti. Erityisen korkea sydämenpysähdyksen riski on sairaalahoidossa olevilla potilailla sekä tavallisella vuodeosastolla että myös teho-osastolla. Maailmassa tapahtuu noin 10000 sydämenpysähdystä päivittäin, näin ollen sydämenpysähdyksen taloudellinen vaikutus on kiistaton.

Tämän tutkimuksen tavoitteina oli arvioida systemaattisesti julkaistua kirjallisuutta tehohoidossa olevien potilaiden sydämenpysähdyksestä, selvittää ennuste ja hoitoon liittyvät kustannukset suomalaisilla teho-osastoilla hoidetuilla sydämenpysähdyspotilailla ja arvioida tehohoitopotilaiden hoitointensiteetin nousun ja tehohoidon aikaisen sydämenpysähdyksen itsenäiset vaikutukset potilaiden kuolemanriskiin pohjautuen Suomen Tehohoitokonsortion, Väestörekisterikeskuksen ja Kansaneläkelaitoksen potilastietokantoihin.

Systemaattisen kirjallisuuskatsauksen perusteella todettiin, että suurin osa teho-osastoilla tapahtuvaa sydämenpysähdystä käsittelevistä tutkimuksista oli retrospektiivisia ja peräisin yhdestä keskuksesta. Teho-osastolla tapahtuvan sydämenpysähdyksen esiintyvyys ja siihen liittyvä kuolleisuus vaihtelivat laajalti tutkimusympäristöstä ja potilasaineistosta riippuen.

Suomalaisilla teho-osastoilla jokaista 1000 tehohoitojaksoa kohti oli 29 sydämenpysähdystä ja sydämenpysähdyksen jälkeinen sairaalakuolleisuus oli 56%.

Sydämenpysähdystapahtumaan ja heikkoon tehohoitojaksoa edeltävään toimintakykyyn liittyvät sairaalakuolleisuusriskit olivat keskenään verrannollisia. Lisäksi korkeampi kuolleisuusriski liittyi myös varhaiseen hoitointensiteetin nousuun erityisesti potilailla, joiden kuolleisuusriski oli arvioitu matalaksi sairauden vaikeusasteen perusteella tehohoitojakson alussa.

Ison suomalaisen yliopistollisen sairaalan teho-osastoilla hoidetuista sydämenpysähdyspotilaista 58% sairaalan ulkopuolella elvytetyistä, 41% sairaalan sisällä elvytetyistä ja 39% teho-osastolla elvytetyistä oli elossa vuoden kohdalla primääristä sydämenpysähdystapahtumasta. Näistä 88-94% selvisi myös neurologisesti hyvin. Hoitokustannukset yhtä vuoden kohdalla elossa olevaa sydämenpysähdyspotilasta kohti olivat 94688 euroa ja yhtä neurologisesti hyvin selvinnyttä potilasta kohti 102722 euroa. Hoitokustannukset olivat verrattavissa muiden tehohoidon potilasryhmien hoitokustannuksiin, joita pidetään yleisesti hyväksyttävinä.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Efendijev I, Nurmi J, Castren M, Skrifvars MB. **Incidence and outcome from adult cardiac arrest occurring in the intensive care unit: a systematic review of the literature**, *Resuscitation* 2014;85:472–479.

II Efendijev I, Raj R, Reinikainen M, Hoppu S, Skrifvars MB. **Temporal trends in cardiac arrest incidence and outcome in Finnish intensive care units from 2003 to 2013**, *Intensive Care Medicine* 2014;40:1853–1861.

III Efendijev I, Raj R, Skrifvars MB, Hoppu S, Reinikainen M. **Increased need for interventions predicts mortality in the critically ill**, *Acta Anaesthesiol Scand* 2016;60:1415–1424.

IV Efendijev I, Folger D, Raj R, Reinikainen M, Pekkarinen PT, Litonius E, Skrifvars MB. **Outcomes and healthcare-associated costs one year after intensive care-treated cardiac arrest**, *Resuscitation* 2018;131:128–134.

The publications are referred to in the text by their Roman numerals. The original publications have been reprinted with the permission of the copyright holders.

ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
AUC	Area under the receiver operating characteristic curve
CA	Cardiac arrest
CAHP	Cardiac Arrest Hospital Prognosis
CI	Confidence interval
CPC	Cerebral Performance Category
CPR	Cardiopulmonary resuscitation
DNAR	Do not attempt resuscitation
ECPFN	Effective costs per survivor with favourable neurological outcome
ECPS	Effective cost per survivor
EEG	Electroencephalography
EHR	Electronic health record
EMS	Emergency medical system
EWS	Early warning score
FICC	Finnish Intensive Care Consortium
GDP	Gross domestic product
ICU	Intensive care unit
ICU-CA	In-ICU cardiac arrest
IHCA	In-hospital cardiac arrest
IQR	Interquartile range
MeSH	Medical subheading
MET	Medical emergency team
MODS	Multiple Organ Dysfunction Score
MRI	Magnetic resonance imaging
NEMS	Nursing Manpower Use Score
NRI	Net reclassification improvement
NSE	Neuron-specific enolase
OHCA	Out-of-hospital cardiac arrest
OPC	Overall Performance Category
OR	Odds ratio
PEA	Pulseless electrical activity
QALY	Quality-adjusted life-year
ROSC	Return of spontaneous circulation
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
SII	Social Insurance Institution of Finland
SOFA	Sequential Organ Failure Assessment
SSEP	Short-latency somatosensory-evoked potential
TH	Therapeutic hypothermia

TISS	Therapeutic Intervention Scoring System
TTM	Targeted temperature management
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHO/ECOG	World Health Organisation/Eastern Cooperative Oncology Group

1 INTRODUCTION

Cardiac arrest (CA), a sudden and devastating event, affects numerous lives annually. Historically, post-CA prognosis was considered grim, with only a fraction of initial CA victims recovering to their pre-arrest level. To improve post-CA outcomes, the concept of 'chain of survival', introduced in 1991, was widely implemented [1]. This concept encompassed the idea of an effective and uninterrupted initial treatment based on four major links: early access, early cardiopulmonary resuscitation (CPR), early defibrillation and early advanced treatment. Strengthening these links resulted in the improvement of post-CA survival regionally [2,3]. Over the past two decades, 'chain of survival' underwent only minor changes, retaining its original integrity. In the early 2000s, therapeutic hypothermia (TH), another crucial change in the treatment of CA, entered into clinical practice [4]. Whilst the role of TH remains controversial, it is possible that TH, along with the advanced resuscitation guidelines for special circumstances published during the 2000s, further strengthened the 'chain of survival' and its fourth link in particular, leading to additional improvements in post-arrest outcomes [5–8].

With an estimated 350,000 to 700,000 sudden CA events yearly in Europe alone, it is clear that CA poses an enormous socioeconomic burden to modern society [9,10]. Eventually, humanity will need to face the reality of limited resources. Thus, it is essential to establish a firm understanding of the healthcare-associated costs and cost-effectiveness regarding CA patients as well.

Originally, CA was stratified according to the initial rhythm based on the rationale of a certain aetiology–treatment pathway. CA stratification by location allows us to view the matter from an alternative perspective, paying more attention to patients' peri-arrest conditions. Whilst the features of out-of-hospital cardiac arrest (OHCA) are well-established, in-hospital CA (IHCA) and in-ICU CA (ICU-CA) in particular have received less attention. A firm belief amongst clinicians persists, whereby outcomes following ICU-CA are viewed as generally very poor. In truth, given a complete physiological failure due to acute disease or a poor preadmission functional status, even the most effective and optimally timed CPR attempts would be of very limited value. By contrast, in-hospital patients, specifically ICU patients, are susceptible to the adverse effects of in-hospital treatments. In such cases, timely intervention to restore patients' physiological stability would make more sense clinically.

2 REVIEW OF THE LITERATURE

2.1 Cardiac Arrest

Key Messages

- CA is an abrupt loss of spontaneous circulation potentially leading to end-organ damage and death.
- CA is categorised based on the initial rhythm (shockable vs non-shockable) and on location (out-of-hospital vs in-hospital).
- More than 3.6 million CAs occur annually worldwide, with most adult CAs resulting from a cardiac aetiology.
- Post-CA syndrome results from ischemia/reperfusion injury and is a key factor in the pathophysiology of CA-induced organ damage.
- CA treatment is complex and time-sensitive, often requiring an intensive care setting.

2.1.1 Definitions

CA is an abrupt loss of circulation due to the cessation of cardiac mechanical activity [11,12]. When left untreated, CA will result in the prompt loss of consciousness, end-organ damage and, eventually, death. CA is not an individual disease, but rather a pre-mortal pathological state. The clinical presentation of CA varies depending on aetiology, duration of the circulatory failure and the presence and extent of CA-induced organ failure.

The return of spontaneous circulation (ROSC) is defined as the restoration of a spontaneous perfusing cardiac rhythm, leading to regaining a palpable pulse, a measurable blood pressure or spontaneous breathing as indicators of successful resuscitation. Time to ROSC marks the delay in restoring signs of circulation in the absence of on-going chest compressions [12].

Initial CA rhythms are stratified into two groups: shockable and non-shockable. Shockable rhythms fall into two categories. Ventricular fibrillation (VF) represents a continuous desynchronised contraction of the ventricular muscle mass as a result of disorganised electrical activity, whilst ventricular tachycardia (VT) is a regular improper excitation of the ventricular muscle mass due to the abnormal conduction of an electrical impulse. Non-shockable rhythms include pulseless electrical activity (PEA), a state of electromechanical dissociation characterised by the conducted electrical impulse of the heart resulting in an insufficient or absent heart muscle contraction. Asystole, also a non-shockable rhythm, is defined as the complete absence of both an electrical impulse and mechanical activity of the heart [13].

2.1.2 Classification

CA is traditionally classified according to two variables: an initial cardiac rhythm (shockable vs non-shockable) and the location of occurrence (out-of-hospital vs in-hospital). The rationale behind the cardiac rhythm–based classification lies in determining the initial treatment and diagnostic approach taken [14,15]. Location-based classification, however, is based on the understanding that IHCA patients might have multiple comorbidities potentially influencing resuscitation outcomes, thereby differing from the majority of OHCA patients [16]. Yet, the availability of advanced life support is typically better and delays to treatment initiation are shorter for IHCA patients [17].

ICU-CA represents a subgroup of IHCA. Still, notable differences exist in peri-arrest factors amongst ICU-CA compared to the remainder of IHCA patients. Specifically, ICU patients are continuously monitored, advanced treatment resources are readily available and delays to initial CA treatment are virtually non-existent. However, ICU patients are also generally sicker and more vulnerable to treatment-associated adverse events than other in-hospital patients [18–20].

2.1.3 Aetiology

Cardiovascular diseases stand as the leading causes of death globally [21,22]. Approximately 40% of all deaths under the age of 75 result from a cardiovascular pathology, with coronary heart disease responsible for 60% to 70% of all sudden cardiac deaths [23,24]. Furthermore, roughly 60% to 80% of OHCAs primarily result from a cardiac pathology, most commonly ischaemic heart disease, followed by other cardiovascular causes, such as structural heart disease and primary arrhythmias [25–28]. Non-cardiac causes, such as trauma, bleeding, pulmonary embolism, asphyxia and drug-overdose, are responsible for the remainder of OHCAs [25,29].

In addition, cardiac disease represents the most common cause of IHCAs, responsible for 50% to 60% of arrests. Hypoxia and pulmonary pathologies cause approximately 15% to 20% of IHCAs, followed by less common aetiologies, such as thrombosis, cardiac tamponade, hypovolemia and sepsis [30–32].

2.1.4 Epidemiology

The estimated incidence of CA varies from between 30 and 100/100,000 person-years for OHCA and from 1 to 6/1000 hospital admissions annually for IHCA. These figures can be extrapolated to establish estimates of 350,000 to 700,000 sudden CAs annually in Europe, 300,000 to 500,000 CAs annually in the US, over 2.5 to 4 million CAs annually in Asia and 20,000 to 30,000 sudden CAs annually in Australia and New Zealand [9,10,33–38]. With an average of 78 OHCAs per 100,000 person-years and 2.2 IHCAs per 1000 hospital admissions, CA incidence in Finland is similar to that in other countries [39,40].

Yet, the incidences of VF/ VT OHCA continue to decrease, possibly due to the increased placement of implantable cardiac defibrillators, improved treatment and more

active primary prevention of coronary heart disease [41–45]. However, an increase in non-cardiac OHCAs has also been recently noted [46].

Whilst the epidemiology of OHCA has received extensive attention, data on in-hospital arrest remain limited. Nearly half of all IHCAs occur in ICU settings [47–49]. Yet, ICU-CA has received little attention thus far, and most of the ICU-CA data are based on single-centre studies [50].

2.1.5 Initial cardiac rhythms

Approximately 25-50% of OHCAs have VF as the initial CA rhythm on the first assessment, although prevalence of shockable rhythms has declined over the past several decades [39,43,51–55]. Yet, the prevalence of initial shockable rhythms can exceed 70% if the rhythm is recorded soon after collapse [56,57].

Despite potentially shorter delays in the initiation of CPR and initial rhythm analysis, the reported prevalence of shockable rhythms in IHCA patients varies from 23% to 51%, which is quite similar to OHCA [17,47,58–60].

2.1.6 Post-cardiac arrest syndrome

CA induces global hypoperfusion, leading to generalised ischaemia; ROSC, if achieved, causes reperfusion. A whole-body ischaemia and subsequent reperfusion results in post-CA syndrome, a condition unique in its definable cause, time course and typical set of pathological processes described as early as the 1970s [61–63]. Furthermore, post-CA syndrome includes a combination of symptoms, such as post-CA brain injury, post-arrest myocardial dysfunction, a systemic ischaemia–reperfusion response and persistent precipitating pathology.

2.1.6.1 Post-cardiac arrest brain injury

CA-related brain injury occurs within the first minutes of ischaemia since the brain is the most ischaemia-sensitive organ. Brain injury involves numerous and complex damage mechanisms, including excitotoxicity, altered calcium homeostasis, the formation of free radicals, pathological protease cascades, activation of cell-death signalling pathways, microcirculatory failure and the malregulation of cerebral blood flow [64–68] Post-arrest factors that may influence the development of brain injury are hyperoxia, hypocapnia, pyrexia, hyperglycemia and seizures [69–74].

2.1.6.2 Post-cardiac arrest myocardial dysfunction

Haemodynamic instability and arrhythmias are common features of the early post-resuscitation period. Post-CA myocardial dysfunction can be detected through appropriate monitoring within minutes after ROSC, and is characterised by the significant impairment of the left ventricle's contractile function. Post-CA myocardial dysfunction manifests as a decrease in the ejection fraction, an elevated left ventricle end-diastolic pressure and a low

cardiac output. The effect is not associated with a reduced coronary blood flow or on-going myocardial ischaemia, but rather represents a stunning phenomenon transient in nature and responsive to inotropic drugs [75–79].

2.1.6.3 Systemic ischaemia–reperfusion response

A whole-body ischaemia–reperfusion injury resulting from CA induces a sepsis-like syndrome through the activation of immunologic and coagulation pathways, resulting in the high risk for multiple organ failure [80]. Endothelial injury, endotoxin release and various cytokines precipitate an early post-arrest pro-inflammatory process and the activation of coagulation pathways [81,82]. The stress of post-arrest ischaemia–reperfusion significantly impacts adrenal function, potentially contributing to the development of refractory shock [83].

2.1.6.4 Persistent precipitating pathology

The clinical course of the post-CA period is often complicated by a pre-existing acute pathology, such as acute coronary disease, thromboembolic condition, sepsis or trauma. Yet, other conditions should be readily considered whenever based on the patient history and clinical presentation. Various pre-existing conditions may require a specific treatment approach coordinated with post-CA organ support [84].

2.1.7 Post-arrest treatment

Treating post-CA patients remains complex and time-sensitive, occurring both in- and out-of-hospital and involving multiple healthcare teams at different stages. Irrespective of the cause of CA, hypoxemia, ischaemia and reperfusion may evolve into multiple organ failure. Whilst the severity of post-CA syndrome varies across patients, effective post-CA treatment should consist of reversing the pathophysiological processes of the syndrome and identifying and treating the initial precipitating pathology. Due to the complexity of post-CA treatment, initial management of CA patients typically takes place in the intensive care setting. The latter involves general ICU monitoring, often with either protocol-based or on-demand advanced haemodynamic and neurological monitoring [84,85].

2.1.7.1 Intensive care

ICU is a specialised environment in the hospital setting that provides optimal and adequate care of patients with severe and life-threatening illnesses and injuries. Intensive care patients receive close and extensive monitoring of basic bodily functions and are under constant observation by highly trained ICU nurses. In addition, ICUs feature a higher nurse-to-patient ratio compared to other hospital wards. Moreover, ICUs possess advanced medical equipment sufficient to support critically ill patients' organ systems, such as mechanical ventilation, renal replacement therapy and advanced monitoring devices. Some specialised ICUs also utilise extracorporeal life support devices and equipment to support patients with acute hepatic failure [86].

2.1.7.2 Specific treatment

Depending on the severity of the post-CA syndrome, the extent of organ damage and the nature of the precipitating condition, individual patients will require different degrees of specialised care and treatment procedures. Post-CA treatment often requires acute cardiovascular interventions and haemodynamic support [87,88], targeted temperature management and active avoidance of hyperthermia [89–91], neurological care [92], glucose control [93,94] and mechanical ventilation to ensure adequate carbon dioxide removal and oxygenation [95–98].

2.2 Outcomes Following Cardiac Arrest

Key Messages

- Post-CA survival varies from 3% to 80% depending upon patient population and local settings.
- Post-CA neurological recovery continues for months and most hospital survivors achieve a favourable neurological outcome.
- The early prognosis of post-CA outcomes must be multimodal and based on an accurate clinical examination and additional diagnostic tools.
- Outcome prediction scores are generally of limited value in post-CA prognostication.

Since the rediscovery of modern cardiopulmonary resuscitation in the 1950s, numerous studies sought to predict outcomes after resuscitation. Older publications regarding both OHCA and IHCA patients suffered from the universal problem of inconsistent reporting [99–102]. A uniform standard for reporting research on OHCA emerged in 1991, followed by two revisions in 2004 and 2014 [11,12,103]. Similarly, the Utstein-style reporting standard for IHCA studies appeared in 1997 [16]. Both recommendations provide a strong basis for CA research, allowing for the systematic comparison of CA-related studies. According to the Utstein guidelines, survival to hospital discharge or survival to 30 days should stand as the minimum measurement of the outcome reported and, preferably, should include data on six-month and one-year outcomes. In addition, evaluation of the neurological outcome of hospital survivors should include an estimate using a simple validated neurological score, such as the Cerebral Performance Category (CPC), the Overall Performance Category (OPC) or a modified Rankin Scale, as well as ideally, an estimate of the post-CA quality of life [103–105].

2.2.1 Survival after OHCA

According to studies published following the emergence of the OHCA Utstein guidelines, survival to hospital discharge for OHCA patients varies between 3% and 10%; yet, some regions have achieved hospital survival of 20% to 40% [9,10,33,39,41,54,106–108]. Survival to hospital discharge for ICU-treated OHCAs approaches 50% [6,109]. In addition, one-

year survival for all-rhythm OHCAs lies between 3% and 22% [110–113]. However, survival for OHCAs with shockable rhythms is significantly better, with 20% to 60% of patients alive at hospital discharge [39,54,107,109] and at least 30% of patients alive at one year after CA [39,112].

2.2.2 Survival after IHCA

Approximately 6% to 22% of IHCA patients survive to hospital discharge [47,48,50,59,114,115]. One-year survival varies between 5% and 29% [102,114]. Similar to OHCAs, hospital survival following IHCA is better for patients with shockable rhythms, reaching 20% to 42% [47,58–60,116]. IHCA patients also exhibit higher survival rates if CA occurs on a weekday (hospital survival 17% vs 20%) and during the daytime (hospital survival 15% vs 20%) [117].

2.2.3 Survival after ICU-CA

Depending on the study population, hospital survival after ICU-CA varies from 0% to 79% [18,118]. For instance, two major multicentre studies reported hospital survival after ICU-CA of 16% [50,119]. Yet, 70% of post-cardiac surgery ICU-CA patients were alive at one year, although mortality in the mixed-ICU population was significantly higher, with only 2% surviving to one year after ICU-CA [118,120,121].

2.2.4 Neurological and functional outcomes

Most studies report neurological outcomes such as CPC or OPC in accordance with the Utstein guidelines [12,16]. Both evaluation systems are directly comparable and define a favourable outcome as CPC/OPC scores of 1 to 2 and unfavourable outcomes as CPC/OPC scores of 3 to 5 (see Table 1) [11,34].

Amongst hospital survivors, a good neurological outcome is achieved in 70% to 93% of OHCAs, 50% to 86% of IHCAs and 77% to 83% of ICU-CAs [48,50,60,109,111,117,122–125]. Although CPC represents the most widely used tool to evaluate neurological outcomes following CA, some concern exists regarding overestimating favourable neurological survival, whereby a significant number of patients with CPC 1 to 2 exhibit a marked cognitive dysfunction [126–129]. The timing of the optimal evaluation of neurological and functional outcome remains unclear. However, some evidence suggests that recovery continues for at least months after the initial arrest, thus indicating the need for repeated evaluation during the recovery process [130,131]. Table 2 summarises the published incidence and outcome estimates for CA patients based on CA location.

Table 1. Outcome of Brain Injury: The Glasgow-Pittsburgh Cerebral Performance and Overall Performance Categories

Cerebral Performance Categories	Overall Performance Categories
1. Good cerebral performance. Conscious. Alert, able to work and lead a normal life. May have minor psychological or neurological deficits (mild dysphasia, nonincapacitating hemiparesis, or minor cranial nerve abnormalities)	1. Good overall performance. Heathy, alert, capable of normal life. Good cerebral performance (CPC1) plus or only mild functional disability from noncerebral organ system abnormalities.
2. Moderate cerebral disability. Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dressing, travelling by public transportation, and preparing food). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia or permanent memory or mental changes.	2. Moderate overall disability. Conscious. Moderate cerebral disability alone (CPC 2) or moderate disability from noncerebral system dysfunction alone or both. Performs independent activities of daily life (dressing, travelling, and food preparation). May be able to work part-time in sheltered environment but disabled for competitive work.
3. Severe cerebral disability. Conscious. Dependent on others for daily support because of impaired brain function (in an institution or at home with exceptional family effort). At least limited cognition. Includes a wide range of cerebral abnormalities from ambulatory with severe memory disturbance or dementia precluding independent existence to paralytic and able to communicate only with eyes, as in the locked-in syndrome.	3. Several overall disability. Conscious. Severe cerebral disability alone (CPC 3) or severe disability from noncerebral organ system dysfunction alone or both. Dependent on others for daily support.
4. Coma, vegetative state. Not conscious. Unaware of surroundings, no cognition. No verbal or psychological interactions with environment.	4. Same as CPC 4.
5. Death. Certified brain dead or dead by traditional criteria.	5. Same as CPC 5.

CPC, Cerebral Performance Categories.

Table is adopted from Cummins et al. Circulation, vol. 84, 1991, pp. 960–75 with permission from Wolters Kluwer Health®

Table 2. Cardiac arrest incidence and post-arrest outcomes stratified by cardiac arrest location

	OHCA	IHCA	ICU-CA
Incidence	30–100/100,000 person-years	1–6/1000 hospital admissions	variable
Hospital survival	3–40% (20–60% for VF/VT)	6–22% (20–42% for VF/VT)	0–79%
One-year survival	3–22%	5–29%	2–70%
Neurological outcome at hospital discharge	70–93% CPC 1–2	50–86% CPC 1–2	77–83% CPC 1–2

OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; ICU, intensive care unit; ICU-CA, in-ICU cardiac arrest; VF/VT, ventricular fibrillation or ventricular tachycardia; CPC, Cerebral Performance Category

2.2.5 Prediction of outcome

Most deaths during the first three days following CA occur due to acute cardiovascular failure [132,133]. Amongst patients surviving to ICU admission, 60% of OHCAs and approximately 25% of IHCAs die during the same hospital stay as a result of post-CA brain injury [132–135]. The most common cause of death in patients with an anticipated poor outcome is the withdrawal of life-sustaining therapy [133,136]. This practice renders the existence of reliable prediction tools and established prognostic protocols essential.

Several studies have proposed factors possibly affecting survival. Some of these factors carry a clear relationship with post-CA outcomes, whilst the effect others remains more vague.

2.2.5.1 Pre-arrest factors

Several studies identified pre-arrest factors associated with outcomes following CA. These include an advanced age, poor cardiac health and diabetes, metastatic cancer, sepsis, renal failure, stroke and a homebound lifestyle [137–141]. Additionally, the socioeconomic environment may associate with post-CA survival. For instance, a low socioeconomic status significantly decreased the chance of receiving CPR in the case of an arrest according to two studies from Asia and the US, although it is unclear whether these findings can be extrapolated to other geographic areas [142,143].

2.2.5.2 Intra-arrest factors

Both a prolonged interval from collapse to the initiation of CPR and a prolonged time to ROSC carry an undisputed association with a poor outcome. Other factors associated with poor outcomes following CA include poor adherence to CPR guidelines, a low intra-arrest end-tidal carbon dioxide level, long preshock pauses and extensive interruptions in assessing the rhythm or providing ventilation, as well as an initial cardiac rhythm of asystole [84].

2.2.5.3 Clinical predictors

Neither pre- nor intra-arrest factors' association with poor outcome is strong enough to serve as an independent prediction tool. Thus, resuscitation guidelines advocate for the practice of multimodal prognostication that includes clinical examination, electrophysiological investigation, diagnostic imaging and biomarkers. [85,135].

Clinical signs associated with poor outcomes include the bilateral absence of a pupillary light reflex 72 h after ROSC, a bilaterally absent corneal reflex and an absent or extensor motor response 72 h after ROSC [144,145]. Both the corneal reflex and motor response can be suppressed by sedatives and neuromuscular blockers; thus, suspicion of residual sedation and paralysis mandates prolonging the observation period. Myoclonus is another clinical entity with a well-established association with poor outcome. A myoclonic status within 48 h of ROSC strongly predicts an unfavourable neurological outcome, yet there are several case reports of good neurological outcome despite that association. [146]

Whilst clinical examination is inexpensive and easy to conduct, the results are also readily visible to treatment teams, thus possibly influencing clinical decisions and ultimately resulting in a 'self-fulfilling prophecy' [135]. Electrophysiological investigations, specifically short-latency somatosensory-evoked potentials (SSEPs) and electroencephalography (EEG), have proved useful as prediction tools in post-arrest comatose patients. For instance, the bilateral absence of N20 SSEP waves predicts a poor outcome with a high positive predictive value [147]. Furthermore, the absence of an EEG reactivity predicts a poor outcome, although the lack of standardisation and a modest inter-rater agreement pose considerable limitations to its clinical application. In patients treated with therapeutic hypothermia (TH), the presence of an EEG-confirmed status epilepticus during TH or after rewarming, as well as a late persistent burst-suppression pattern, often precede a poor outcome [148,149]. In addition, cerebral oedema and a reduced grey-to-white matter ratio on a head CT scan predict a poor outcome [150]. Magnetic resonance imaging (MRI) can improve the predictive value due to its high sensitivity in identifying an ischaemic brain injury. Furthermore, MRI can help identify extensive anoxic changes despite normal results using other predictors [151]. A series of serum biomarkers have been evaluated as predictors of a poor outcome after CA. Neuron-specific enolase (NSE) carries the most extensive scientific basis for its use as a predictor, although it is highly influenced by haemolysis and neuroendocrine tumours [152]. Some evidence suggests that the discriminative value of NSE improves at 48 and 72 h following arrest and any increase in NSE levels between two time points may carry an additional predictive value [153].

2.2.5.4 Outcome prediction scores

Different severity-of-illness scores are used widely in the prediction of outcomes for ICU patients. [154,155] The most commonly used scores are the Acute Physiology and Chronic Health Evaluation score (APACHE) with its three revisions[156–159] and Simplified Acute Physiology Score (SAPS) with its two revisions. [160–163] Both APACHE and SAPS predict the risk of mortality based on data from the first day of ICU stay. In addition, there is a number of repetitive severity-of-illness scores that rely on data collected daily, either for the first three days or throughout an ICU stay [154]. The most notable repetitive scores are the Sequential Organ Failure Assessment (SOFA) score and the Multiple Organ Dysfunction Score (MODS) [164,165].

Notably, APACHE II and APACHE III scores had only modest prediction performance for mortality and neurological outcome in both OHCA and IHCA. [166–168]. With moderate discrimination abilities, neither SAPS II nor SAPS 3 performed better than specific intra-arrest predictors and should not be used as prediction tools for post-CA outcomes [169,170]. Several studies found that cardiovascular and renal components of the SOFA score associated with the outcome after CA; however, the usefulness of the SOFA score as an outcome predictor in CA patients remains unclear [171,172]. No systematic evaluation of MODS as an outcome predictor after CA has been performed so far.

All of the abovementioned severity-of-illness models were developed for a general ICU population. Thus, they lack CA-specific data, such as time delays, initiation of bystander CPR and the initial cardiac rhythm. Furthermore, several CA-specific scores were developed for early post-CA outcome prediction. For instance, the OHCA score was developed to predict neurological functioning after successful resuscitation in unselected OHCA patients upon hospital admission. This score includes the initial cardiac rhythm, the 'no-flow' and 'low-flow' time intervals as well as the serum creatinine and lactate measurements. The OHCA score initially showed good discriminative abilities on both the development [area under the receiver operating characteristic curve (AUC) = 0.82] and validation cohort (AUC = 0.88), and a good calibration [173]. Despite these findings, the specificity of the OHCA score remained low and the performance of the model could not be reproduced in later studies, suggesting a poor predictive power for the score [167,173–175]. The Cardiac Arrest Hospital Prognosis (CAHP) score was developed in France, and is based on the Sudden Death Expertise Centre registry for the early prediction of unfavourable neurological outcomes, defined as a CPC score of 3, 4 or 5 in OHCA patients at hospital discharge [176]. The CAHP score implements nomogram with seven independent predictors: age, a non-shockable rhythm, time from collapse to basic life support, time from the initiation of basic life support to ROSC, home-setting arrest, epinephrine dose and arterial pH. The score demonstrated excellent discriminative abilities (AUC = 0.93) in the development cohort and a good to excellent discrimination in two external validation cohorts (AUC = 0.85 and 0.91, respectively). However, according to the authors, the CAHP score has not been validated beyond the French healthcare system [176]. More recently, the Targeted Temperature Management (TTM) score emerged [177]. This score is intended for the early prediction of survival and neurological outcomes at six months in comatose OHCA patients with a presumed cardiac cause of arrest and was developed from the TTM trial cohort. The TTM score includes ten independent predictors: age, home-setting arrest, a non-shockable rhythm, duration of the no-flow and low-flow periods, administration of epinephrine, the bilateral absence of corneal and pupillary reflexes, a Glasgow Coma Score motor response of 1, arterial pH and the carbon dioxide level. The TTM score demonstrated a good discriminative performance in the validation cohort (AUC = 0.84). However, the authors did not perform an external validation of the TTM score. Notably, both the OHCA and CAHP scores showed only a fair discrimination in the same TTM trial–based cohort [177]. None of these three specific CA prediction scores is applicable to IHCA patients. Since multiple post-arrest factors influence the outcome of CA, the clinical utility of outcome predictions on admission remains questionable, rendering the abovementioned scores invalid for clinical decision-making for individual patients.

An alternative to severity-of-illness scores are activity-based scores. One of the most extensively used activity-based scores is the Therapeutic Intervention Scoring System (TISS). TISS, originally introduced in 1974, was suggested by its authors as an indicator of patients' clinical condition [178]. The original TISS-76 underwent revision in 1981 and eventually, after modernisation, evolved into TISS-28 [179,180], the latter serving as the

basis for the Nursing Manpower Use Score (NEMS) [181]. Although originally suggested as a severity-of-illness index, TISS and its variations currently serve as widely accepted tools to measure nursing workload and consistent means of describing ICU costs [181,182].

2.3 Healthcare-Associated Costs and Cardiac Arrest

Key Messages

- Caring for critically ill patients remains expensive.
- Cost-effectiveness and cost-utility represent the preferred measures for estimating costs in critical care settings.
- Health economic analyses ideally should include estimates of both direct and indirect costs.
- A frequently cited incremental cost-effectiveness ratio of US$50,000 per quality-adjusted life-year (QALY) likely underestimates societal willingness to pay for health benefits.
- Data on CA-related healthcare costs remain limited to several single-centre studies.
- Public access defibrillation and therapeutic hypothermia are considered as cost-effective interventions.

Critical care is generally considered an expensive and resource-demanding specialty [183]. In 2010, critical care medicine costs in the US reached over US$4000 per in-patient day, or a total of US$108 billion per year, accounting for 13% of all hospital costs, 4% of national healthcare expenditures and 0.7% of the US gross domestic product (GDP). [184] From 2000 to 2010, the costs of critical care medicine nearly doubled, with further increases expected [184].

2.3.1 Assessment of costs in critical care

Four major types of cost analyses have been used to assess the economic impact of medical interventions in healthcare settings. These consist of cost-minimisation, cost-benefit, cost-effectiveness and cost-utility analyses.

2.3.1.1 Cost-minimisation

In cost-minimisation analysis, medical interventions with comparable indications and outcomes are evaluated in order to identify the least expensive option. The analysis requires the preselection of interventions with clinically equivalent outcomes [185]. This type of analysis is relatively easy to perform; however, it is not recommended for critical care settings due to the complexity of critical care patients and its inability to assess relationships across tested interventions related to outcomes and risks [186].

2.3.1.2 Cost-benefit

A cost-benefit analysis compares the costs and benefits of different interventions by assigning a monetary value to measure an effect. Both benefits and costs are expressed in monetary terms and include a time-value adjustment. The analysis has three general approaches: the human capital approach, which involves measuring costs assumed to be related to outcomes; the revealed preferences approach, which relies on observing an individual's behaviour as an estimate of a benefit; and the contingent valuation approach, which uses the reported willingness to pay as a measure of assumed benefits [185,187].

2.3.1.3 Cost-effectiveness

A cost-effectiveness analysis evaluates the costs of resources spent on a specific intervention in order to achieve an intended outcome. Contrary to the cost-benefit analysis, outcomes are measured on a one-dimensional score, such as life-years gained, number of deaths avoided and number of ICU admissions. This type of analysis does not require the assignment of monetary values to outcomes and takes into account different types of costs. The primary limitations of the cost-effectiveness analysis include the need for sensitivity analyses or incremental cost-effectiveness ratios in order to avoid misinterpretations when comparing outcomes for alternative treatment options [185,187]. A specific type cost-effectiveness measure is the effective cost per survivor (ECPS), measured as the total cost for survivors and non-survivors within a specific group divided by the number of survivors within the same group [188].

2.3.1.4 Cost-utility

A cost-utility analysis, similar to a cost-effectiveness analysis, also estimates the ratio between the costs of an intervention and the benefit produced. However, the benefit of the intervention is measured in terms of the number of years lived in full functional health. The most common measure of outcomes in cost-utility analyses is the quality-adjusted life-year (QALY), a metric that corresponds to one year lived in a hypothetical state of 'perfect health'. This type of analysis represents the preferred method in the estimation of ICU-related costs due to its more patient-centred approach and its ability to compare outcomes across different types of interventions [185,189].

2.3.2 Types of costs

Health economists distinguish between two major types of costs. Direct costs include the costs of all resources (that is, treatment and diagnostic procedures, medications and personnel work hours) consumed in order to achieve the desired clinical outcomes. By contrast, indirect costs refer to the loss of resources due to lost productivity or the need for additional payments (that is, sick leave, disability pension and the loss of national taxes) resulting from specific clinical outcomes [188]. Whilst direct costs are typically extensively reported, quantification of indirect costs remains a much more complex task often requiring robust approximations.

2.3.3 Acceptable costs for healthcare interventions

The most frequently cited incremental cost-effectiveness threshold for the justification of a medical intervention is US$50,000 in the US [190]. The corresponding thresholds vary from £20,000 to £30,000 in the UK and €80,000 in the Netherlands [183,191,192]. However, some researchers believe that these monetary thresholds do not correlate with society's willingness to pay and are, in fact, too low [193–195]. More recent estimates suggest applying values between US$100,000 and US$300,000 per QALY with the simultaneous use of several thresholds instead of a single value being more appropriate [193,194].

2.3.4 Cardiac arrest-related costs

The exact CA-related consumption of resources and expenses remains unknown and, thus far, only a limited number of publications have addressed the matter. Due to differences in methodology and the lack of uniform reporting guidelines, estimated costs are highly variable. Most publications evaluate treatment-associated costs for OHCAs [196–200]. Thus, only a few studies report treatment-associated costs for IHCAs, either as a separate patient population or clustered with OHCAs [201,202]. Furthermore, most studies report either hospital costs or hospital and pre-hospital costs, with only one study reporting post-hospital costs [199]. Yet, one recent study on CA-related healthcare costs reported a steady increase in CA treatment–related expenses [203]. Whilst data on the overall cost-effectiveness of CA treatment remain lacking, the implementation of public access defibrillation and TH in witnessed VF OHCAs are considered cost-effective interventions [204,205].

3 PURPOSE OF THE STUDY

This study aimed to investigate the outcomes and healthcare-associated costs of CA patients treated in Finnish ICUs, focusing specifically on the following objectives:

1) To systematically review earlier studies on ICU-CA, to determine the incidence and hospital mortality of ICU-CA in Finnish ICUs and to investigate outcomes and healthcare-associated costs in ICU-treated CA patients. (studies I, II and IV)

2) To study the association of early treatment intensity and specific therapeutic interventions and the administration of CPR related to hospital mortality in Finnish ICU patients (study III).

4 SUBJECTS AND METHODS

4.1 Study Setting and Population

Study I consists of a systematic review of the literature. Studies II through IV are based on the Finnish Intensive Care Consortium (FICC) database and include ICU patients from all participating FICC hospitals from 2003 through 2013 (II, III) and from a single tertiary teaching hospital from 2005 through 2013 (IV). Table 3 summarises the key characteristics of the studies.

Table 3. Basic characteristics of the studies

	Study I	Study II	Study III	Study IV
Study design	Systematic review of the literature	Retrospective, registry-based	Retrospective, registry-based	Retrospective
Data source	PubMed, CINAHL, Cochrane Database	FICC	FICC	Multiple databases (FICC, SII, MH, FPRC)
Study period	1990–2013	2003–2013	2003–2013	2005–2014
Endpoints of the study	ICU-CA incidence and outcomes in the literature	ICU-CA incidence and hospital mortality in Finland	Impact of treatment intensity on hospital mortality of Finnish ICU patients	One-year survival, neurological outcome and healthcare costs of ICU-treated CA patients

FICC, Finnish Intensive Care Consortium; SII, the Social Insurance Institution of Finland; MH, Meilahti Hospital; FPRC, Finnish Population Register Centre, CINAHL, Cumulative Index to Nursing and Allied Health Literature; CA, cardiac arrest; ICU, intensive care unit, ICU-CA, in-ICU cardiac arrest.

4.1.1 Finnish Intensive Care Consortium (II, III, IV)

FICC, a cooperative benchmark project established in 1994, aims to improve the quality of intensive care in Finland. FICC comprises 22 acute care hospitals' ICUs covering mainland Finland and over 90% of the Finnish population. The FICC database prospectively collects demographic, treatment-specific and severity-of-illness data. Physiological data are obtained directly from ICU clinical information systems that collect data automatically from patient monitors, ventilators and laboratory systems. ICU staff manually enter information on comorbidities, the type of admission, diagnoses and vital status at ICU and hospital discharge. Subsequently, collected data undergo a multilevel validation process that includes the automatic filtering of technical artefacts and manual validation by local, specially trained personnel [6,206].

For substudies II through IV, the FICC database provided data on preadmission physical status according to the modified World Health Organization/Eastern Cooperative

Oncology Group (WHO/ECOG) classification implemented by FICC (see Table 4) [207], admission diagnoses, common activity and severity-of-illness scores and components, as well as data on hospital mortality, age, gender and length of ICU and hospital stays.

Table 4. Modified ECOG performance status implemented by FICC

Grade	Performance status
0	Able to carry out work or equal (retired).
1	Ambulatory and capable of all self-care, but unable to carry out any work activities.
2	Partially dependent. Needs help in self-care.
3	Fully dependent. Cannot carry on any self-care.

ECOG, Eastern Cooperative Oncology Group; FICC, Finnish Intensive Care Consortium. Table adopted from Oken MM, Am J Clin Oncol 1982;5:649–55 with permission from Wolters Kluwer Health®

4.1.2 Finnish healthcare and social security system (IV)

Finland has a predominantly public healthcare system funded by the government, municipalities and private or government-subsidised insurance companies. The Social Insurance Institution of Finland (SII) is a government agency that administers all social security funds in Finland. The Finnish Population Register Centre is a government agency that provides demographic information to Finnish residents, public administrations, businesses and communities. The database of the Finnish Population Registry Centre collects data on every birth or death event for each Finnish resident. Every Finnish citizen and every person residing in Finland permanently has a unique personal identification number. Every. Furthermore, every Finnish resident is also entitled to full social security.

The Finnish mainland is divided into 20 hospital districts. Each district has its own major hospital, identified as the central hospital. There are 15 non-university central hospitals; each hospital has one adult ICU that, in many cases, also treats children older than infant-age. Five university hospitals have major ICUs with a mixed profile of patients. However, Helsinki University Hospital also has four specialised ICUs–specifically, neurosurgical, trauma, cardiosurgical and paediatric–which were not members of FICC during the study period.

4.1.2.1 Meilahti Hospital (IV)

Meilahti Hospital is the largest of the Helsinki University Hospitals. Meilahti Hospital functions as the primary referral centre for all CA patients in the greater Helsinki area and the Hospital District of Helsinki and Uusimaa, with a combined population of approximately 1.6 million. At the beginning of the study period, Meilahti Hospital had four ICUs: surgical ICU, general mixed ICU, cardiosurgical ICU and medical ICU. Subsequently, the surgical and mixed ICUs were combined into a single unit. All ICUs except for the cardiosurgical ICU were members of FICC during the entire study period.

4.1.3 Definition of cardiac arrest (II, IV)

The FICC database does not collect CA-specific data. Thus, CA patients were identified as follows. Patients with an admission diagnosis of CA according to APACHE III admitted to ICUs from hospital emergency departments represented the OHCA group; patients with an APACHE III admission diagnosis of CA admitted to ICUs from general wards, diagnostic or procedural units, operating room or post-anaesthesia care units were classified as the non-ICU IHCA group; and finally, patients with a positive value of TISS-76 'cardiac arrest and/or countershock within 48 h' and an APACHE III admission diagnosis other than CA formed the ICU-CA group.

4.1.4 Intensive care unit cardiac arrest in Finnish ICUs (II)

This substudy included all adult (≥18 years) ICU admissions from the FICC database treated between 2003 and 2013. Patients with an admission diagnosis of CA according to APACHE III were excluded from the analyses as out-of-ICU CAs. Here, ICU-CA was defined according to the above-mentioned criteria. All other admissions were counted as non-CAs. Mortality analyses included only the initial ICU admission and only the first CA event for patients with multiple ICU stays and/or multiple CAs during the same hospital stay. APACHE III admission diagnosis-based subgroup analyses were performed for post-cardiac surgery and neurosurgical or neurological admissions.

4.1.5 Healthcare-associated costs and outcomes after ICU-treated cardiac arrest (IV)

This substudy's population included all OHCA, IHCA and ICU-CA patients treated at Meilahti Hospital ICUs between 2005 and 2013. CA patients were initially identified from the FICC database according to the abovementioned CA definition, and were cross-checked with Meilahti Hospital's electronic health records (EHRs). Only the initial ICU admission and the first CA event were included in this substudy.

4.1.6 Treatment intensity and mortality amongst ICU patients (III)

This substudy included all adult ICU patients with a length of ICU stay ≥ 3 days from all participating FICC hospitals between 2003 and 2013. All patients with missing data were excluded. For the purpose of mortality analyses only the first ICU admission was considered.

4.2 Data Collection

4.2.1 Systematic literature review (I)

A systematic search of previous research (published from 1 January 1990 through 31 December 2012) on ICU-CA was performed in January 2013 using PubMed, CINAHL and the Cochrane Database of Systematic Reviews. The search included the following medical

subheadings (MeSHs): 'heart arrest' AND 'intensive care unit' OR 'critical care' OR 'critical care nursing' OR 'monitored bed' OR 'monitored ward' OR 'monitored patient'. Following the initial database search, the articles were screened based on the title and/or abstract and checked for the inclusion and exclusion criteria (see Table 5) and duplicates according to the PRISMA guidelines [208]. Only studies published in English language were included. Quantitative analyses were deliberately omitted due to the marked heterogeneity of the reviewed studies' populations.

Table 5. Inclusion and exclusion criteria applied to the ICU-CA publications (study I)

Inclusion criteria
Studies focused on ICU-CA
Adult patients
ICU-CA incidence and/or outcome data reported
Exclusion criteria
Studies focused on out-of-ICU CA only
Paediatric patients
Duplicate publications

ICU, intensive care unit; CA, cardiac arrest; ICU-CA, in-ICU cardiac arrest.

After the initial search and screening process, publications focused on incidence and outcomes of in-ICU cardiac arrest in adults were accepted for detailed review. A customised quality assessment score was developed to evaluate the methodological quality of the selected articles. The quality assessment scoring included the type of study, characteristics of the study setting and population, as well as specific CA data such as the definition of CA, time to ROSC, initial cardiac rhythm, post-CA outcomes and data on special resuscitation techniques (Table 6). The maximum quality assessment score of 22 indicated an excellent methodological quality of the study, whilst the minimum score of 0 corresponded to a poor quality study. The definition of CA and estimation of incidence and survival rates were in accordance with the in-hospital Utstein guidelines [16]. Post-CA survival included the initial survival defined as survival ≥24 h, survival to ICU discharge, survival to hospital discharge and long-term survival defined as survival for six months or longer. A good neurological outcome was defined as a CPC score of 1 and 2 or the ability of the survivor to complete everyday activities either independently or with minimal help [11,104]. Two authors evaluated the selected articles' methodological quality according to the customised quality assessment score. Agreement between the reviewers' assessments was measured using a weighted kappa score. Any disagreement between two initial reviewers was resolved through discussion after an additional independent review by a third author.

Table 6. Evaluation criteria for methodological quality of the studies included in the systematic review of the literature (I)

Evaluation criteria	points max. 22
1. Study type Focused prospective study (4 points) Prospective resuscitation registry (3 points) Prospective ICU registry (2 points) Retrospective (1 point)	4
2. ICU definition/staffing reported	1
3. General ICU/patient profile outlined	1
4. Cardiac arrest incidence: cardiac arrest/ICU admission	2
5. Cardiac arrest clearly defined	1
6. Initial arrest rhythm reported	1
7. Cardiac arrest aetiology reported	1
8. Initial ICU admission diagnosis	1
9. Time intervals (1 point each) Time to initiation of CPR Time to ROSC	2
10. Reporting of clinical factors found to correlate with the occurrence of CA (e.g. changes in physiological parameters, acute illness scoring systems, etc.)	1
11. Outcome data (1 point each) 24h survival ICU discharge Hospital discharge Long-term survival (minimum 180 days)	4
12. Neurological outcome (1 point) or quality of life (1 point) after hospital discharge	2
13. Data on special resuscitation techniques and unconventional treatment strategies (e.g. open-chest CPR)	1

ICU, intensive care unit; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation. Table reprinted from Efendijev I, Resuscitation 2014;85:472–9 with permission from Elsevier®

4.2.2 Intensive care unit cardiac arrest in Finnish ICUs (II)

All required data for the substudy were obtained from the FICC database. Primary outcomes consisted of the incidence of ICU-CA calculated as the ratio of ICU-CA events to the total number of ICU admissions, whilst hospital mortality was calculated as the percentage of ICU-CA non-survivors taken from the total number of ICU-CA events.

4.2.3 Healthcare-associated costs and outcomes in ICU-treated cardiac arrest patients (IV)

Initially, CA patients treated in Meilahti Hospital's ICUs were identified through the FICC database. Subsequently, based on the personal identification numbers, patients were matched with the databases of the Finnish Population Register Centre and the Social

Insurance Institution of Finland. In addition to the data provided by FICC, CA-specific data were obtained from Meilahti Hospital's EHRs. These data included the specific CA location, the initial cardiac rhythm, time to ROSC and the neurological outcome at one year after CA according to CPC. Total healthcare-associated costs consisted of the hospital costs, rehabilitation costs and social security costs. Hospital costs were calculated as the costs for the entire treatment period, including costs of personnel, surgery, diagnostic procedures, the ICU stay and the general ward stay. Hospital costs were obtained directly from Meilahti Hospital's billing records. In addition, rehabilitation costs were calculated by multiplying the length of the stay on the rehabilitation unit by the daily cost on the designated care unit based on a report from the Finnish National Institute for Health and Welfare [209]. The Social Insurance Institution of Finland database provided data on the social security costs, which consisted of disability allowances, sickness allowances, private physician and physiotherapist costs, prescription drug costs and medical transport expenses.

4.2.4 Treatment intensity and mortality amongst ICU patients (III)

The data required for this substudy were obtained from the FICC database. Early treatment intensity was described as the sum of the daily TISS-76 points for the first three ICU days. Changes in the early treatment intensity were calculated as the difference in the daily TISS-76 score between day three and day one (ΔTISS). Significant therapeutic interventions were defined as TISS items of 3 and 4 points. Standard interventions, such as 'arterial line placement' and 'intravenous boluses', were excluded, as well as TISS items characteristic of the specific patient population (Tables 7a and 7b).

Table 7a. TISS 4-point items included in study III

TISS 4-point items	Prevalence in the study population (%)
Cardiac arrest and/or countershock within 48 h	9
Controlled ventilation with or without PEEP	47
Controlled ventilation with intermittent or continuous muscle relaxants	24
Pulmonary artery catheter	31
Atrial or ventricular pacing	6
Haemodialysis in unstable patient	14
Induced hypothermia	5
Pressure-activated blood infusion	3
Platelet transfusion	14
Emergency operative procedures (within past 24 h)	29
Emergency endoscopy or bronchoscopy	19
Vasoactive drug infusion (>1 drug)	41

TISS, Therapeutic Intervention Scoring System; PEEP, positive end-expiratory pressure.

Table 7b. TISS 3-point items included in study III

TISS 3-point items	Prevalence in the study population (%)
Central IV hyperalimentation (includes renal, cardiac, hepatic failure fluid)	49
Chest tubes	24
IMV or assisted ventilation	71
CPAP	47
Concentrated K^+ infusion via central catheter	75
Nasotracheal or orotracheal intubation	32
Complex metabolic balance (frequent intake and output)	93
Multiple ABG, bleeding and/or STAT studies (>4 shift)	57
Frequent infusion of blood products (>5 units/24 h)	8
Vasoactive drug infusion (1 drug)	77
Continuous antiarrhythmic infusions	21
Cardioversion for arrhythmia (not defibrillation)	8
Hypothermia blanket	26
Acute digitalisation – within 48 h	11
Measurement of cardiac output by any method	34
Active diuresis for fluid overload or cerebral oedema	72
Emergency thora-, para- and peri-cardiocenteses	7
Active anticoagulation (initial 48 h)	78
Coverage with more than 2 IV antibiotics	29

TISS, Therapeutic Intervention Scoring System; IV, intravenous; IMV, intermittent mandatory ventilation; CPAP, continuous positive airway pressure; ABG, arterial blood gas; STAT, *statim.*

4.3 Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics for Mac, versions 22.0, 23.0 and 24.0 (IBM Corp, Armonk, NY, USA), R: A Language and Environment for Statistical Computing (R-Foundation for Statistical Computing, Vienna, Austria) with 'PredictABEL' [210] and 'pROC' [211] packages, and Stata Statistical Software for Mac OS (StataCorp LP, College Station, TX, USA).

The chi-squared test (two-tailed) was used for categorical univariate analyses. Most of the continuous data were highly skewed, thus necessitating the use of the Mann-Whitney U-test in the majority of calculations. The Student's t-test was used for normally distributed data. Categorical data are presented as absolute numbers (percentages), continuous nonparametric data as medians [interquartile range (IQR)] and parametric data as means [standard deviations (SDs)], unless stated otherwise.

Several severity-of-illness models were developed using multivariate logistic regression to evaluate temporal changes in outcomes and to estimate the independent effect of treatment intensity and specific therapeutic interventions on hospital mortality (Table 8). Furtherrmore, risk-adjusted mortality rates were calculated for each year as the ratio between the observed and predicted outcomes, thereby representing the outcome rate if

the patient case-mix remained identical over time (II). The performance of the case-mix adjusted models was assessed using discrimination [area under the receiver operating characteristic curve (AUC)] and calibration using the Hosmer-Lemeshow *C* statistic (II and IV) [212,213]. The differences in AUCs were estimated using the bootstrap-based test, and improvement in a model's performance was defined as the difference in AUC (ΔAUC) with a corresponding p value of < 0.001 (III) [210,211,214–216]. Additionally, improvement to a customised model's performance was estimated using the continuous net reclassification improvement (NRI) [217,218]. Where applicable, the variance inflation factor (VIF_{max}) was calculated to test for collinearity between the included predictor variables (II and III).

Associations between variables and categorical outcomes were determined using binary logistic regression analysis through calculation of the odds ratios (ORs) with 95% confidence intervals (CIs) (II–IV). Associations between explanatory variables and continuous dependent variables, such as costs, TISS scores and length of stay, were assessed through estimating the coefficients of a multivariate linear regression (IV). The threshold for statistical significance was determined as p-value < 0.001 (II, III) and < 0.05 (IV) depending on the size of the study populations.

All healthcare-associated costs were adjusted to the 2013 consumer price index (CPI) in Finland in euro (€) using the following formula (IV):

$$CPI\ adjusted\ cost = Cost * \frac{CPI\ in\ 2013}{Admission\ year\ CPI}$$

Cost-effectiveness was calculated as the sum of total healthcare-associated costs in the respective patient group divided by the number of survivors for ECPS and by the number of survivors with a favourable neurological outcome for ECPFN (effective costs per survivor with a favourable neurological outcome) within the respective group of patients. Due to the descriptive nature of study IV, sensitivity analyses were not applicable when evaluating the cost-effectiveness.

Table 8. Variables included in the baseline severity-of-illness models

Study II	**Study III**	**Study IV**
Age	Age	Age
Preadmission physical status*	Preadmission physical status*	Simplified preadmission physical status (independent vs not independent)
Admission year	–	Admission year
Admission type (emergency vs elective)	Admission type (emergency vs elective)	–
Admission type (non-operative vs post-operative)	Admission type (non-operative vs post-operative)	Initial cardiac rhythm
APACHE III diagnosis class (cardiological vs non-cardiological)	–	Time to ROSC
SAPS II score (admission type, cardiovascular and age points subtracted)	SAPS II score (admission type, comorbidity and age points subtracted)	SAPS II score (comorbidity and age points subtracted)
SOFA score (cardiovascular points subtracted)	–	–
Any severe chronic comorbidity according to APACHE II	Any severe chronic comorbidity according to APACHE II or SAPS II	Any severe chronic comorbidity according to APACHE II or SAPS II

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; ROSC, return of spontaneous circulation; SOFA, Sequential Organ Failure Assessment.
*A modified World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) classification implemented by FICC.

5 RESULTS

5.1 Previous Publications on Intensive Care Unit Cardiac Arrest (I)

The initial literature search identified 794 citations; one article was manually included, and three articles were added via a cross-reference search. After screening for exclusion and inclusion criteria, the study included eighteen original publications. The lowest quality assessment score was 6 and the highest was 16; nine publications received 10 or more points. The weighted kappa score showed only a fair (0.339) agreement between two initial reviewers.

All of the studies were published between 1990 and 2013. Five studies were prospective; amongst these, three were prospective studies focused specifically on ICU-CA, one was based on a prospective ICU registry and one was based on a prospective resuscitation registry ('Get with the Guidelines Registry') [50,118,123,167,219]. The remaining consisted of retrospective and single-centre studies (Table 9) [18–20,120–122,220–226].

CA was uniformly defined as the cessation of circulatory function resulting in the initiation of CPR. The aetiology of ICU-CA varied from cardiac to septic with no obvious pattern, although only six studies reported aetiology-related data. According to thirteen studies reporting initial cardiac rhythms, in 55% to 84% of cases the initial cardiac rhythm was non-shockable. The time to the initiation of CPR was under 30 seconds [18,19]. In eleven studies the reported time to ROSC varied for hospital survivors from 5 to 65 minutes. Furthermore, ICU-CA incidence ranged from 6 to 78 per 1000 ICU admissions (Table 9). Initial survival (≥24 h) fell between 9% and 90%, whilst hospital survival varied from 0% to 79%. Post-cardiac surgery patients exhibited the highest rate of hospital survival, although one of the two studies on post-cardiac surgery ICU-CA excluded patients with maximum inotropic support, intra-aortic balloon pump and ventricular assistant devices. For neurosurgical patients, survival to hospital discharge varied between 9% and 18% (Table 9). Only nine studies reported data on long-term survival that spanned from 1% for ICU-treated cancer patients up to 69% for cardiac surgery patients with a long-term follow-up period lasting from 6 months to 5 years. Finally, eleven studies mentioned 'do not attempt resuscitation' (DNAR) orders, whereby two studies included a clear description of the local DNAR policy, and two other studies reported the absence of official DNAR policies.

Table 9. Summary of studies selected for the systematic review of the literature (study I)

Study	Study type	Study setting	Study period	Study population	Duration of CPR or time to ROSC	Cardiac arrest incidence per 1000 ICU admissions	Survival to hospital discharge
Tortolani et al. *Resuscitation* 1990	Retrospective	Single centre	NR	158	Duration of CPR in all ICU-CA patients: 39 +/- 26 minutes	NR	14%
Peterson et al. *Chest* 1991	Retrospective	Single centre	1985–1988	114	Time to ROSC in survivors to hospital discharge: 8 +/- 4 minutes	NR	11%
Landry et al. *Arch Intern Med* 1992	Retrospective	Single centre	1987–1988	114	Length of code in survivors to hospital discharge: 12 +/- 10 minutes	NR	5%
Karetzky et al. *Arch Intern Med* 1995	Retrospective	Single centre	1990–1992	360	Duration of CPR in survivors (mean): 14 minutes	NR	13%
Smith et al. *J Am Coll Surg* 1995	Prospective ICU registry	Single centre	1987–1993	55	NR	11	3%
Anthi et al. *Chest* 1998	Prospective	Single centre	1993–1996	29	NR	7	79%
Wallace et al. *Support Care Cancer* 2002	Retrospective	Single centre	1993–2000	406	NR	78	2%
Myrianthefs et al. *Resuscitation* 2003	Retrospective	Single centre	1999–2000	111	NR	NR	0%
Rabinstein et al. *Mayo Clin Proc* 2004	Retrospective	Single centre	1994–2001	21	Duration of resuscitation efforts in survivors: ≤5 minutes	NR	18%
Enohumah et al. *Resuscitation* 2006	Retrospective	Single centre	1999–2003	169	Time to ROSC in survivors: 8 +/- 5 minutes	10	9%
Yi et al. *Neurosurgery* 2006	Retrospective	Single centre	1992–2002	214	Duration of CPR in survivors (mean): 10 minutes	NR	47%
Chang et al. *J Crit Care* 2009	Prospective	Single centre	2004–2006	222	Time to ROSC in survivors (mean): 7 minutes	NR	15%
Guney et al. *J Card Surg* 2009	Retrospective	Single centre	1998–2004	148	NR	NR	17%

Table 9 cont.

Study	Study type	Study setting	Study period	Study population	Duration of CPR or time to ROSC	Cardiac arrest incidence per 1000 ICU admissions	Survival to hospital discharge
Grigoriyan et al. *J Crit Care* 2009	Retrospective	Single centre	2002–2007	83	NR	NR	60%
Tian et al. *Am J Respir Crit Care Med* 2010	Prospective resuscitation registry	Multi-centre	2000–2008	49,656	NR	NR	16%
Kutsogiannis et al. *CMAJ* 2011	Retrospective	Multi-centre	2000–2005	239	Duration of CPR (all patients): mean 20 min, median 14 min	NR	27%
Skrifvars et al. *Resuscitation* 2012	Prospective	Single centre	2008–010	22	Time to ROSC in survivors: median 5 minutes	6	52%
Lee et al. *Acta Anaesthesiol Scand* 2013	Retrospective	Single centre	2009–2010	131	Time to ROSC in survivors (3 months): 9 +/- 13 minutes; in all patients: 18 +/- 20 minutes	13	One-month survival: 24%

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ICU, intensive care unit; ICU-CA, in-ICU cardiac arrest; NR, not reported.

5.2 Intensive Care Unit Cardiac Arrest in Finland

5.2.1 Incidence of ICU-CA in Finnish intensive care units (II)

Between 2003 and 2013, 173,484 ICU admissions were registered in the FICC database. Of these, 8506 (5%) were excluded from the study as out-of-ICU-CAs. Thus, 164,255 ICU admissions were eligible for the incidence analysis. A CA event was documented in 4717 cases, resulting in an overall incidence of 29 ICU-CAs per 1000 ICU admissions. The lowest incidence of ICU-CA occurred in the post-operative non-cardiovascular group, whilst the highest incidence was found in the non-operative cardiovascular group (Table 10). A significant reduction in ICU-CA incidence occurred during the study period (Figure 1).

Table 10. ICU-CA incidence by APACHE III admission diagnosis group

APACHE III diagnosis group	Number of ICU-CA patients	Incidence of ICU-CA n/1000 ICU admissions (95% CI)
Non-operative	3641	39 (37–40)
Cardiovascular and vascular	1414	118 (112–124)
Other non-operative	2227	27 (26–28)
Post-operative	1076	15 (15–16)
Cardiovascular	576	20 (19–22)
Other post-operative	500	12 (11–13)
Total	**4717**	**29 (28–30)**

ICU, intensive care unit; ICU-CA, in-ICU cardiac arrest; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval.

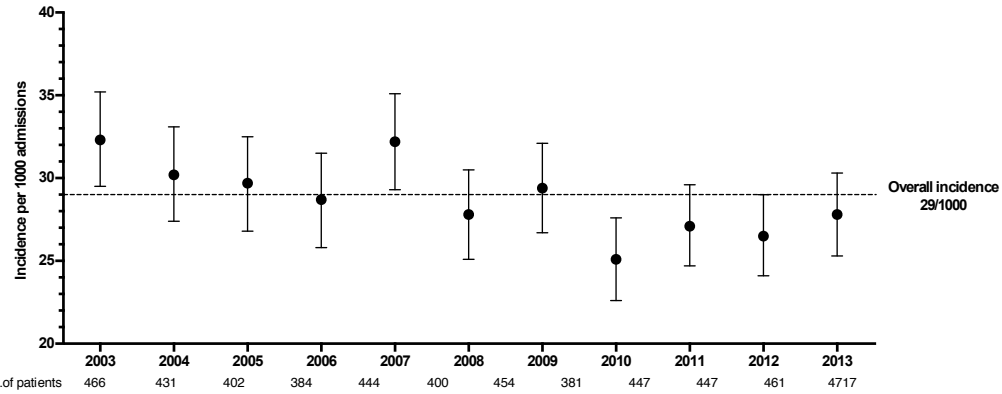

Figure 1. ICU-CA incidence in Finnish ICUs reported as means and 95% confidence intervals. ICU, intensive care unit; ICU-CA, in-ICU cardiac arrest.
Figure adopted from Efendijev I, Intensive Care Med 2014;40:1853–61 with permission from Springer Nature®

5.2.1.1 *Incidence of ICU-CA in Meilahti Hospital ICUs (IV)*

Between 2005 and 2013, 16,705 admissions were recorded in ICUs at Meilahti Hospital. Amongst these, 170 experienced an ICU-CA event, resulting in a crude ICU-CA incidence of 10/1000 ICU admissions.

5.2.2 Hospital mortality after ICU-CA in Finland (II)

To avoid classifying the same patient as dead or alive numerous times, mortality analyses required additional exclusion of all readmissions. Hence, amongst 164,255 ICU admissions eligible for the incidence analyses, 11,057 (6.7%) were excluded as readmissions. Additionally, 3681 (2.4%) admissions were excluded due to missing data. As a result, 149,517 ICU admissions were eligible for mortality analyses. Of 4246 ICU-CA patients, 2355 (56%) did not survive to hospital discharge. Amongst non-CA patients (n = 145,271), a total of 16,625 (11%) died during the same hospital stay. Compared to ICU-CA hospital survivors, ICU-CA hospital non-survivors were older, had more severe preadmission comorbidities, were more severely ill according to all implemented severity-of-illness scores (APACHE II, SAPS II and SOFA) and required more intensive treatment as demonstrated by the higher average daily TISS-76 score (Table 11).

The crude hospital mortality of post-cardiac surgery ICU-CA patients was 33%, whilst for the neurological/neurosurgical ICU-CA population the crude hospital mortality approached 56%. The adjusted severity-of-illness model showed satisfactory performance with AUC = 0.72 for ICU-CA patients and 0.85 for non-CA patients with no significant collinearity between the predictors included (VIF_{max} = 3.331 for ICU-CA and VIF_{max} = 2.769 for non-CA). The standardised mortality ratio was 1.00 (95% CI 0.97–1.03) and the risk-adjusted mortality rate decreased significantly over the study period for both ICU-CA and non-CA patients (Figures 2a and 2b). Over the study period, implementation of any type of treatment limitations increased from 7% to 10% ($p < 0.001$).

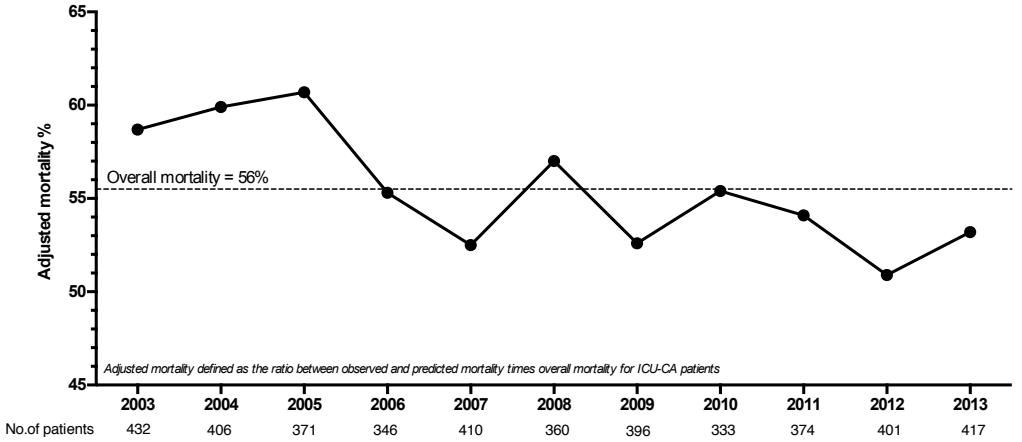

Figure 2a. Adjusted mortality after ICU-CA in Finland, 2003-2013.
ICU, intensive care unit; ICU-CA, in-ICU cardiac arrest.
Figure reprinted from Efendijev I, Intensive Care Med 2014;40:1853–61 with permission from Springer Nature®

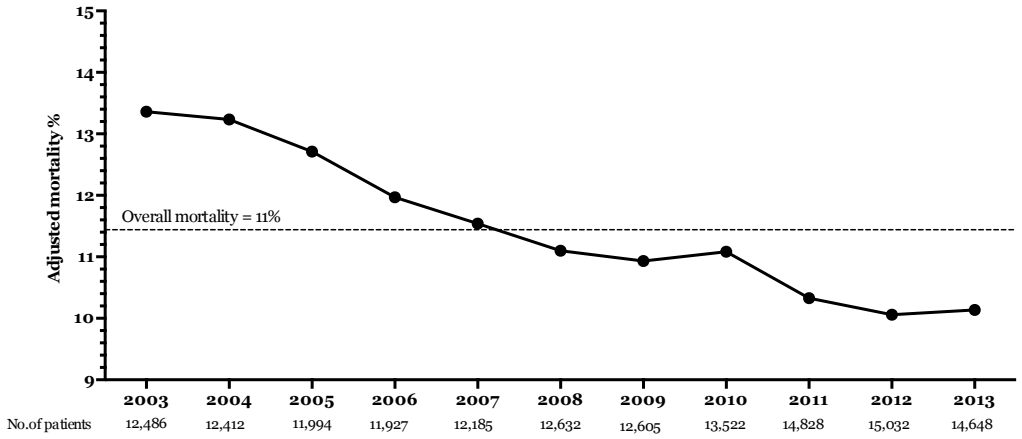

Figure 2b. Adjusted mortality amongst non-CA ICU patients in Finland, 2003-2013.
ICU=intensive care unit, CA=cardiac arrest.

Table 11. Baseline characteristics of ICU-CA survivors vs. ICU-CA non-survivors*

	All ICU-CA patients (N = 4246)	ICU-CA survivors (n = 1891)	ICU-CA non-survivors (n = 2355)	p value
Age	66 (56–75)	65 (54–74)	68 (57–76)	<0.001
Male sex	2782 (66)	1273 (67)	1509 (64)	>0.001
Admission type				
Operative	965 (23)	539 (29)	426 (18)	<0.001
Emergency	3943 (93)	1696 (90)	2247 (95)	<0.001
SAPS II score	55 (40–70)	44 (33–58)	64 (49–77)	<0.001
SAPS II score >52 (binary variable)	2257 (53)	613 (32)	1644 (70)	<0.001
Heart rate, beats/minute	69 (49–127)	70 (55–125)	68 (36–129)	<0.001
Systolic blood pressure	78 (61–90)	84 (75–95)	69 (47–83)	<0.001
Body temperature	37.3 (36.4–38.1)	37.5 (36.8–38.1)	37.1 (36–38)	<0.001
Urinary output, L/day	1.7 (0.6–2.7)	2.1 (1.3–3.1)	1 (0.2–2.2)	<0.001
White blood cell count	12 (8.8–16.5)	11.8 (8.9–16.1)	12.4 (8.8–16.8)	>0.001
Potassium	4.6 (4.1–5.2)	4.4 (4.1–4.9)	4.7 (4.2–5.4)	<0.001
Sodium	140 (137–143)	140 (137–143)	140 (136–143)	>0.001
Bicarbonate	19 (14.1–25)	22.8 (17.3–26)	17 (12.9–23.1)	<0.001
Glasgow Coma Scale (as a continuous variable)	11 (3–15)	14 (6–15)	7 (3–15)	<0.001
SAPS chronic diseases				
AIDS	5 (0.1)	2 (0.1)	3 (0.1)	>0.001
Metastatic cancer	88 (2.2)	32 (1.8)	56 (2.5)	>0.001
Haematologic malignancy	64 (1.6)	13 (0.7)	51 (2.3)	<0.001
SAPS mechanical ventilation	3192 (80)	1378 (76)	1814 (83)	<0.001
APACHE II score	29 (21–36)	24 (18–31)	32 (26–39)	<0.001

Table 11 cont.

	All ICU-CA patients (N = 4246)	ICU-CA survivors (n = 1891)	ICU-CA non-survivors (n = 2355)	p value
APACHE II chronic health status				
Heart failure (NYHA IV)	465 (11)	194 (10.3)	271 (11.5)	>0.001
Liver insufficiency	149 (3.5)	41 (2.2)	108 (4.6)	<0.001
Chronic respiratory disease	546 (13)	199 (11)	347 (15)	<0.001
Chronic renal insufficiency	152 (3.6)	44 (2.3)	108 (4.6)	<0.001
Immunosuppression	252 (5.9)	80 (4.2)	172 (7.3)	<0.001
SOFA score	9 (7–12)	8 (6–10)	10 (8–13)	<0.001
TISS average score on day of admission	37 (31–44)	36 (30–42)	38 (32–46)	<0.001
Significant TISS items on day of admission				
Controlled ventilation	3348 (79)	1474 (78)	1874 (80)	>0.001
Pulmonary artery catheter	1172 (28)	543 (29)	629 (27)	>0.001
Acute/unstable patient's haemodialysis	212 (5)	81 (4.3)	131 (5.6)	>0.001
Chronic/stable patient's haemodialysis	19 (0.4)	8 (0.4)	11 (0.5)	>0.001
Pressure-activated blood transfusion	163 (3.8)	40 (2.1)	123 (5.2)	<0.001
Measurement of cardiac output	1223 (29)	584 (31)	639 (27)	>0.001
Vasoactive drug infusion, >1 drug	1615 (38)	633 (34)	982 (42)	<0.001
Vasoactive drug infusion, 1 drug	1715 (40)	771 (41)	944 (40)	>0.001
Frequent infusion of blood products, >5 units/24 h	313 (7.4)	113 (6.0)	200 (8.5)	>0.001

*Categorical variables n: (%), continuous variables: median (IQR, interquartile ratio).

ICU-CA, in-ICU cardiac arrest; SAPS, Simplified Acute Physiology Score; AIDS, Acquired Immune Deficiency Syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; NYHA, New York Heart Association functional classification; SOFA, Sequential Organ Failure Assessment; TISS, Therapeutic Intervention Scoring System.

Table adopted from Efendijev I, *Intensive Care Med* 2014;40:1853–61 with permission from Springer Nature®.

5.3 Cardiac Arrest Patients in Meilahti Hospital ICUs

In total, 1343 ICU-treated CA patients were identified, of whom 319 (24%) patients were excluded due to incomplete data. As a result, the final study population consisted of 1024 ICU-treated CA patients. Amongst these, 66% were OHCAs and 34% were IHCAs, 21% of whom experienced ICU-CAs. OHCA patients were younger, had a better functional status prior to ICU admission according to the simplified WHO/ECOG classification, fewer severe comorbidities and a lower severity of acute illness upon ICU admission. The initial cardiac rhythm was shockable for the majority of OHCAs, whilst it was either PEA or asystole for the majority of IHCA and ICU-CA patients. However, time to ROSC was considerably shorter for IHCAs and particularly for ICU-CAs (Table 12).

5.3.1 Survival and neurological outcome (IV)

One-year survival was 58% for OHCAs, 41% for IHCAs and 39% for ICU-CA patients. Amongst one-year survivors, 94% of OHCAs, 88% of IHCAs and 93% of ICU-CAs had CPC of 1 or 2. One-year survival did not change significantly between 2005 and 2013, whilst the adjusted favourable neurological outcome improved over the study period for IHCA, but not for OHCA or ICU-CA.

5.3.2 Healthcare-associated costs (IV)

The total sum of healthcare-associated costs for all patients included in the study was €50,847,540. Hospital costs accounted for the majority of total costs (74%), followed by rehabilitation costs (14%) and social security costs (12%). Survivors with a favourable neurological outcome consumed 64% of all costs (over €32 million). The mean total costs were markedly higher for survivors compared to non-survivors and for survivors with an unfavourable outcome compared to survivors with a favourable outcome irrespective of the location of CA or the initial cardiac rhythm. Mean costs grouped by CA location and initial cardiac rhythm are presented in Figures 3 and 4, respectively.

Table 12. Baseline characteristics of the study population

Variables	OHCA (n = 672)	All IHCA (n = 352)	ICU-CA (n = 75)
Age in years, *median (IQR)*	61 (53–69)	64 (56–74)	64 (56–73)
Male sex, *n (%)*	514 (77)	231 (66)	50 (67)
Simplified preadmission physical status*			
Independent, *n (%)*	637 (95)	296 (84)	66 (88)
Non-independent, *n (%)*	35 (5)	56 (16)	9 (12)
Severe comorbidity at the time of ICU admission, *n (%)***	92 (14)	125 (36)	29 (39)
SAPS II, *median (IQR)*	43 (34–57)	52 (39–68)	49 (38–66)
APACHE II score, *median (IQR)*	21 (17–29)	27 (19–34)	26 (18–32)
SOFA score during the first 24 hours, *median (IQR)*	8 (6–10)	10 (8–13)	9 (7–13)
TISS-76 average daily score, *mean (SD)*	37 (8)	36 (9)	41 (9)
Time to ROSC in minutes, *median (IQR)*	20 (14–25)	7 (3–12)	3 (1–8)
Initial cardiac rhythm			
Ventricular fibrillation/ventricular tachycardia, *n (%)*	504 (75)	116 (33)	29 (39)
Pulseless electrical activity	104 (15)	141 (40)	29 (39)
Asystole	49 (7)	66 (19)	10 (13)
Other/unknown	15 (2)	29 (8)	7 (9)
LOS ICU in days, *median (IQR)*	3 (2–4)	3 (1–6)	4 (2–11)
LOS hospital in days, *median (IQR)*	10 (4–19)	10 (4–20)	15 (5–29)
One-year survival, *n (%)*	391 (58)	146 (41)	29 (39)
One-year survival with a favourable neurological outcome, *n (%)*	367 (94)	128 (88)	27 (93)

OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; ICU-CA, in-ICU cardiac arrest; IQR, interquartile range; ICU, intensive care unit; SD, standard deviation; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; TISS-76, Therapeutic Intervention Scoring System 76; ROSC, return of spontaneous circulation; LOS, length of stay.

*A simplified World Health Organization/Eastern Cooperative Oncology Group classification.

**Any severe chronic comorbidity according to APACHE II or SAPS II.

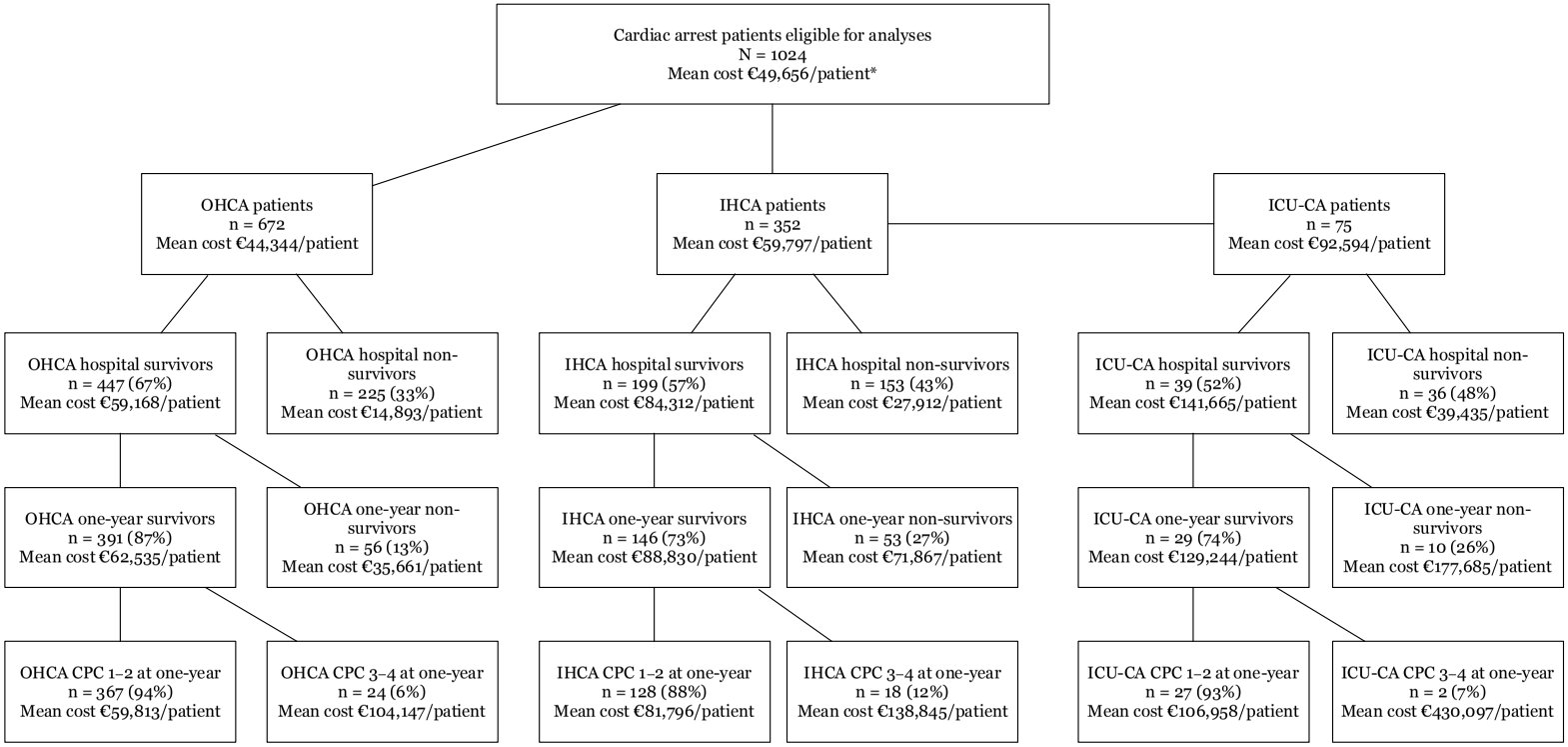

Figure 3. Mean costs per patient stratified by cardiac arrest location.
OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest;
ICU-CA, in-ICU cardiac arrest; CPC, Cerebral Performance Category.
*costs are adjusted to the 2013 consumer price index in Finland in euro (€).
Figure adopted from Efendijev I, Resuscitation 2018;131:128–134 with permission from Elsevier®

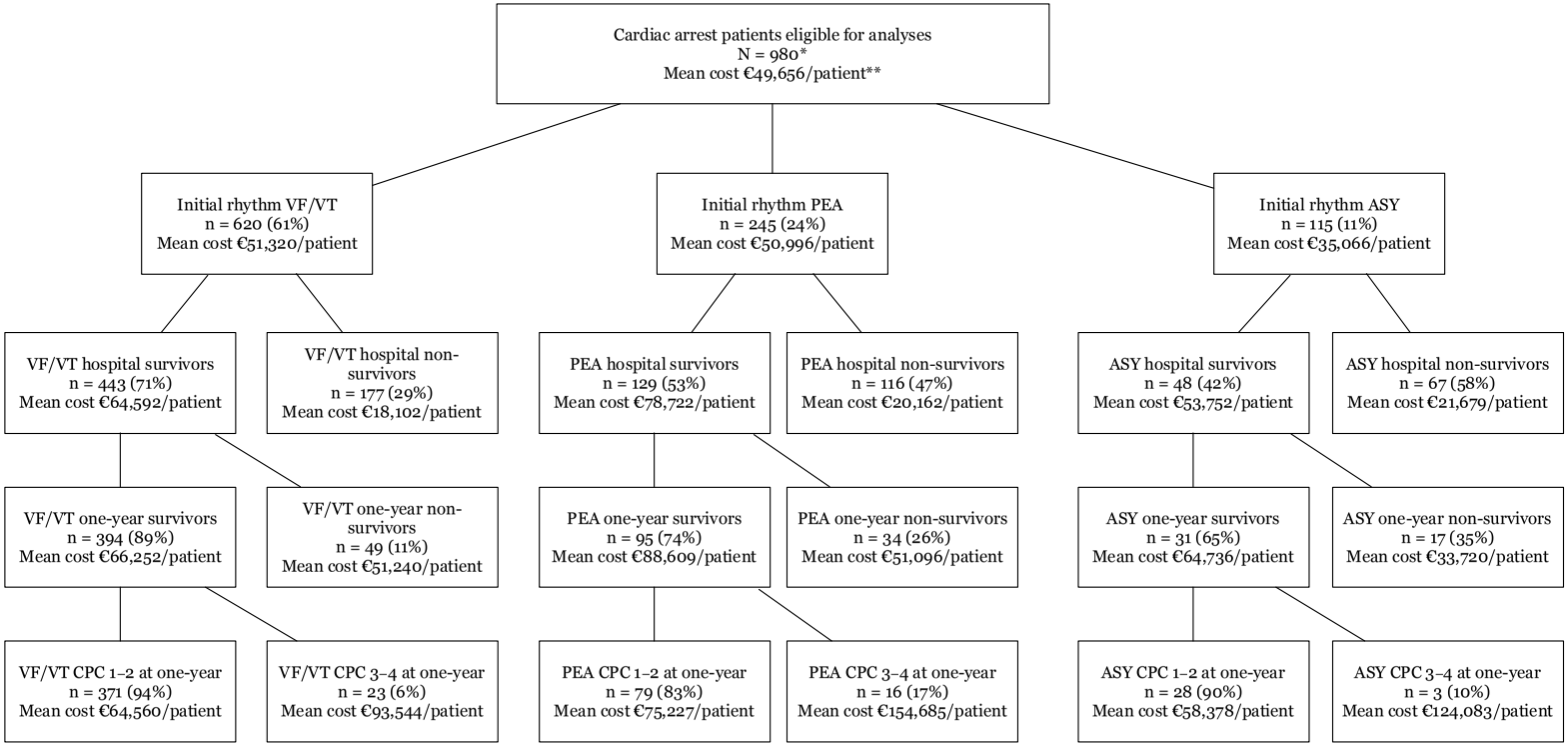

Figure 4. Mean costs per patient stratified by initial cardiac rhythm.
VF/VT, ventricular fibrillation or ventricular tachycardia; PEA, pulseless electrical activity; ASY, asystole; CPC, Cerebral Performance Category.
*patients with 'other' or unknown initial cardiac rhythm were excluded from analysis n=44 (4%)
**costs are adjusted to the 2013 consumer price index in Finland in euro (€).
Figure adopted from Efendijev I, Resuscitation 2018;131:128–134 with permission from Elsevier®

5.3.2.1 *Factors influencing healthcare-associated costs in ICU-treated cardiac arrest patients*

Based on the multivariate linear regression analyses, healthcare-associated costs decreased with asystole, an older age and a higher SAPS II score. For hospital survivors, the effect of asystole and an older age on healthcare-associated costs remained the same. However, a higher SAPS II score had an inverse effect on costs. An in-hospital CA and any severe preadmission comorbidity increased the total costs and some of its components. The most pronounced increase in the total costs resulted from the in-ICU CA location. Finally, the year of admission had no effect on healthcare-associated costs (Table 13 and Figure 5).

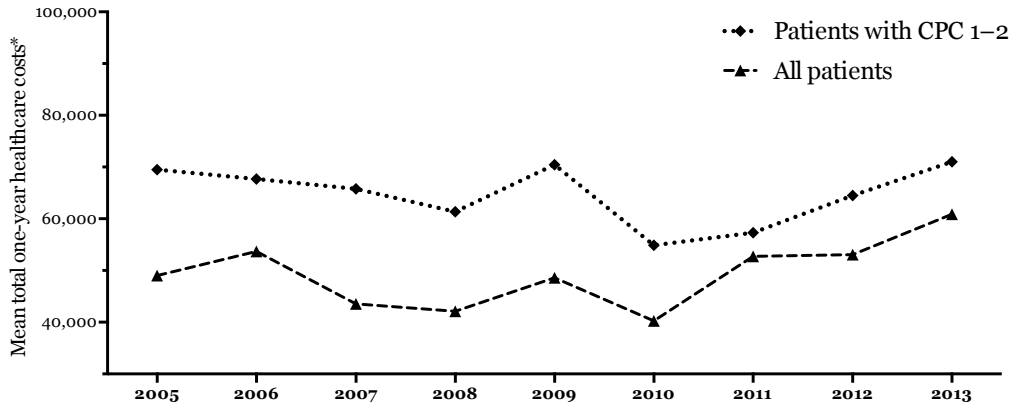

Figure 5. One-year total healthcare-associated costs for ICU-treated CA patients
ICU, intensive care unit; CA, cardiac arrest; CPC, Cerebral Performance Category.
*costs are adjusted to the 2013 consumer price index in Finland in euro (€).

5.3.2.2 *Cost-effectiveness*

ECPS reached €94,688 whilst ECPFN was €102,722 for all patients. The highest effective costs emerged for the ICU-CA group, with ECPS of €239,468 and ECPFN of €257,207, followed by all IHCAs and OHCAs. When stratified by initial cardiac rhythm, the effective costs were highest in the PEA group with ECPS of €94,688 and ECPFN of €106,555, whilst the effective costs for asystole and shockable rhythms remained comparable to one another (Figures 6 and 7).

5.3.2.3 *Treatment intensity and length of stay*

IHCA associated with a significant increase in the case-mix adjusted treatment intensity expressed as the average daily TISS-76 score. Treatment intensity remained highest for the ICU-CA group and lowest for non-shockable rhythms and patients with a non-independent preadmission functional status.

Table 13. Factors associated with healthcare costs based on multivariate linear regression analyses

	Mean change in costs per patient (€)	95%CI (€)		p value
Total costs				
Age*	-420	-671	-168	<0.05
Admission year**	589	-728	1,906	NS
SAPS II score***	-351	-582	-119	<0.05
Severe comorbidity at the time of ICU admission#	10,825	1,942	19,707	<0.05
Preadmission physical status				
Non-independent vs. independent	-10,227	-22,840	2,386	NS
Time to ROSC (min)##	-336	-723	51	NS
Initial cardiac rhythm, VF/VT as reference				
PEA	-4,808	-14,230	4,615	NS
Asystole	-19,976	-32,008	-7,944	<0.05
Location of cardiac arrest, OHCA as reference				
All IHCA	17,974	9,005	26,944	<0.05
ICU-CA	48,448	33,822	63,075	<0.05
Hospital costs				
Age*	-164	-340	11	NS
Admission year**	859	-61	1,778	NS
SAPS II score***	-204	-365	-42	<0.05
Severe comorbidity at the time of ICU admission#	7,139	940	13,338	<0.05
Preadmission physical status				
Non-independent vs. independent	-7,736	-16,538	1,067	NS
Time to ROSC (min)##	-242	-512	28	NS
Initial cardiac rhythm, VF/VT as reference				
PEA	-5,297	-11,873	1,279	NS
Asystole	-15,493	-23,891	-7,097	<0.05
Location of cardiac arrest, OHCA as reference				
All IHCA	14,320	8,060	20,581	<0.05
ICU-CA	36,682	26,487	46,876	<0.05
Rehabilitation costs				
Age*	-68	-174	39	NS
Admission year**	-315	-876	245	NS
SAPS II score***	-54	-152	44	NS

Table 13 cont.

	Mean change in costs per patient (€)	95%CI (€)		p value
Severe comorbidity at the time of ICU admission#	36	-3,739	3,810	NS
Preadmission physical status				
Non-independent vs. independent	-1,015	-6,374	4,344	NS
Time to ROSC (min)##	-71	-235	94	NS
Initial cardiac rhythm, VF/VT as reference				
PEA	1,439	-2,565	5,442	NS
Asystole	-1,818	-6,930	3,295	NS
Location of cardiac arrest, OHCA as reference				
All IHCA	3,255	-557	7,066	NS
ICU-CA	10,926	4,658	17,193	<0.05
Social security costs				
Age*	-188	-235	-140	<0.05
Admission year**	45	-203	295	NS
SAPS II score***	-93	-137	-49	<0.05
Severe comorbidity at the time of ICU admission#	3,650	1,967	5,333	<0.05
Preadmission physical status				
Non-independent vs. independent	-1,476	-3,866	914	NS
Time to ROSC (min)##	-23	-97	50	NS
Initial cardiac rhythm, VF/VT as reference				
PEA	-949	-2,735	836	NS
Asystole	-2,664	-4,944	-385	<0.05
Location of cardiac arrest, OHCA as reference				
All IHCA	399	-1300	2,099	NS
ICU-CA	841	-1,966	3,649	NS

CI, confidence interval; OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; ICU-CA, in-ICU cardiac arrest; ROSC, return of spontaneous circulation;
NS, not significant; VF/VT, ventricular fibrillation or ventricular tachycardia; PEA, pulseless electrical activity.
*For each additional year.
**For each subsequent year.
***For each additional point.
#Any severe chronic comorbidity according to APACHE II or SAPS II.
##For each additional minute.
Table adopted from Efendijev I, Resuscitation 2018;131:128–134 with permission from Elsevier®

Whilst the case-mix adjusted length of ICU stay was longer for IHCAs, no difference was observed in the case-mix adjusted hospital length of stay between OHCAs and all IHCAs. The lengths of both ICU and hospital stays were significantly longer for ICU-CA patients. Furthermore, the initial cardiac rhythm or time to ROSC did not influence the length of ICU stay, whilst the length of hospital stay decreased significantly with an increase in time to ROSC. Dependency in self-care was associated with both longer ICU and hospital stays.

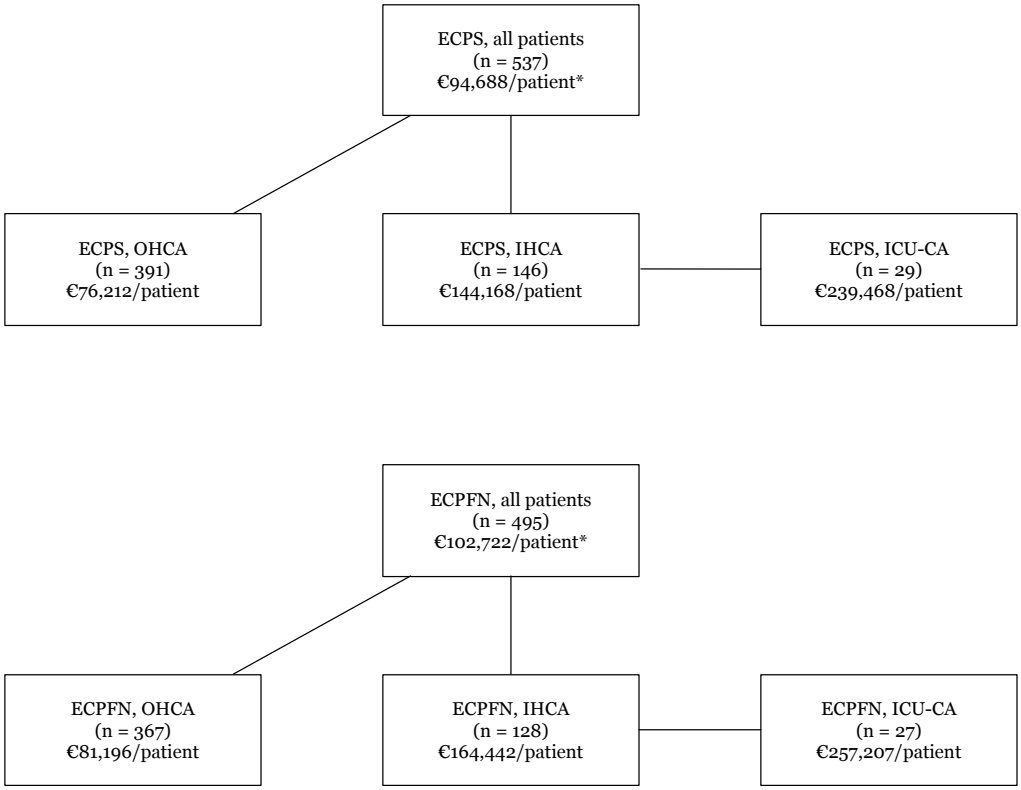

Figure 6. Effective cost per one-year survivor (ECPS) and per survivor with favourable neurological outcome (ECPFN) stratified by cardiac arrest location.
OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; ICU-CA, in-ICU cardiac arrest.
*costs are adjusted to 2013 consumer price index in Finland in euro (€).

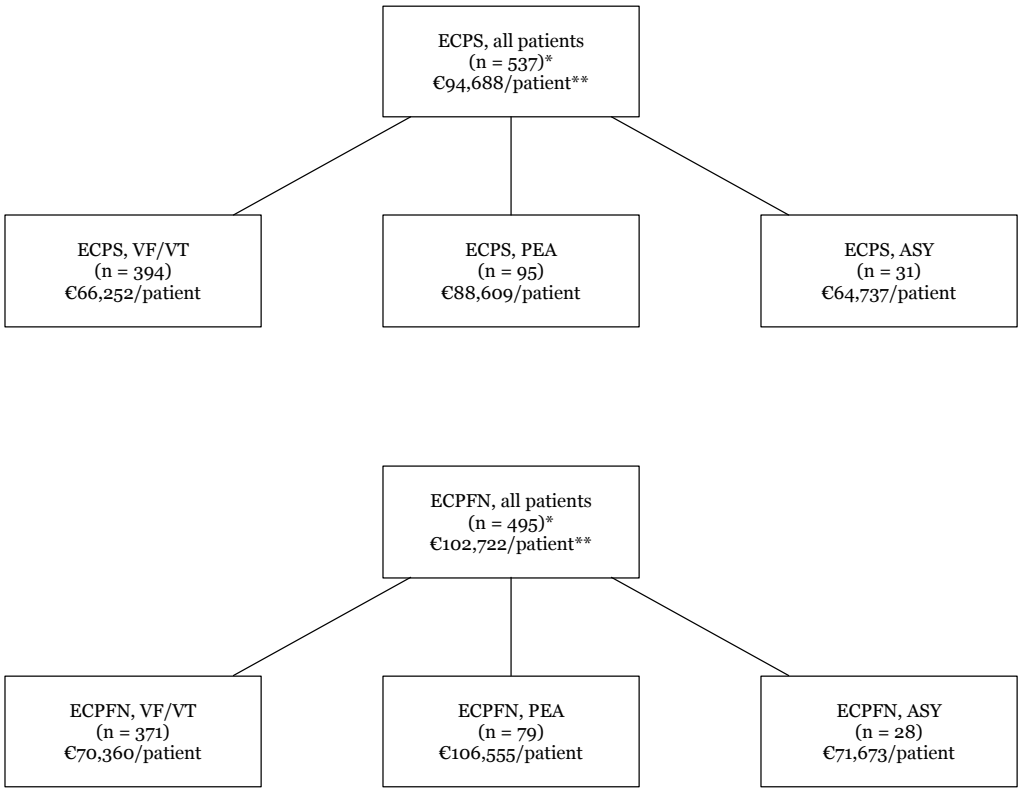

Figure 7. Effective cost per one-year survivor (ECPS) and per survivor with favourable neurological outcome (ECPFN) stratified by initial cardiac rhythm.
VF/VT, ventricular fibrillation or ventricular tachycardia; PEA, pulseless electrical activity; ASY, asystole.
*patients with 'other' or unknown initial cardiac rhythm excluded (n=17).
**costs are adjusted to 2013 consumer price index in Finland in euro (€).
Figure adopted from Efendijev I, Resuscitation 2018;131:128–134 with permission from Elsevier®

5.4 Treatment Intensity and Hospital Mortality in Finnish ICU Patients

Amongst 173,484 ICU admissions identified in the FICC database between 2003 and 2013, a total of 42,493 were eligible for inclusion in this study. The remaining patients were excluded as readmissions, due to missing data or because the length of ICU stay was shorter than 3 days. In total, 34,009 (80%) survived to hospital discharge. According to the univariate analysis, hospital survivors were significantly younger, less severely ill, were more likely capable of independent preadmission functioning (according to WHO/ECOG) and had fewer severe comorbidities before ICU admission.

5.4.1 Association between TISS-76 scores and hospital mortality (III)

The average daily TISS-76 score revealed a significant independent association with an increased risk of hospital mortality. This relationship was linear in the group of patients with a low initial risk of mortality estimated using traditional severity-of-illness scores. Any increase in treatment intensity (ΔTISS > 0) during the first 3 days in ICU was observed for 29% of patients and was associated with a marked increase in the risk of in-hospital death [adjusted OR 1.47 (95% CI 1.40–1.56)]. For those with a substantial increase in the early treatment intensity (ΔTISS ≥ 5), the risk of in-hospital death was even higher [adjusted OR 1.74 (95% CI 1.63–1.87)].

The baseline prediction model (without TISS data) exhibited a satisfactory discrimination with AUC = 0.73 (95% CI 0.72–0.73). Adding the TISS scores to the baseline model improved the discrimination significantly (ΔAUC 0.01–0.02, $p < 0.001$), whilst AUC increased further after adding selected TISS variables (ΔAUC = 0.03, $p < 0.001$). The increase to NRI was most notable in the low risk group (Table 14).

Table 14. Continuous NRI

TISS predictors added to the baseline risk model	Continuous NRI, %				
	All patients	Risk group 1	Risk group 2	Risk group 3	Risk group 4
TISS D1 + ΔTISS	26	41	27	22	19
TISS AVG + ΔTISS	30	49	32	27	25
Select TISS items	41	55	49	38	29

NRI, net reclassification improvement; TISS, Therapeutic Intervention Scoring System 76; TISS D1, sum of TISS points on day 1; TISS AVG, mean daily TISS score for ICU stay; ΔTISS, difference between day 1 and day 3.

Table adopted from Efendijev I, *Acta Anaesthesiol Scand* 2016;60:1415–24 with permission from John Wiley & Sons, Inc®.

5.4.2 Specific treatment interventions and hospital mortality (III)

From all 3- and 4-point TISS items, 11 individual and 2 combined items were included as candidate predictors. Amongst these, 'cardiac arrest and/or countershock within 48 h', 'haemodialysis in unstable patient' and 'major blood transfusion' exhibited the strongest association with an increased risk of hospital death. A WHO/ECOG preadmission functional status "fully dependent" had a comparable effect on the risk of hospital mortality to that of the TISS item 'cardiac arrest and/or countershock within 48 hours', (see Figure 8). The model exhibited no significant collinearity ($VIF_{max} = 1.383$).

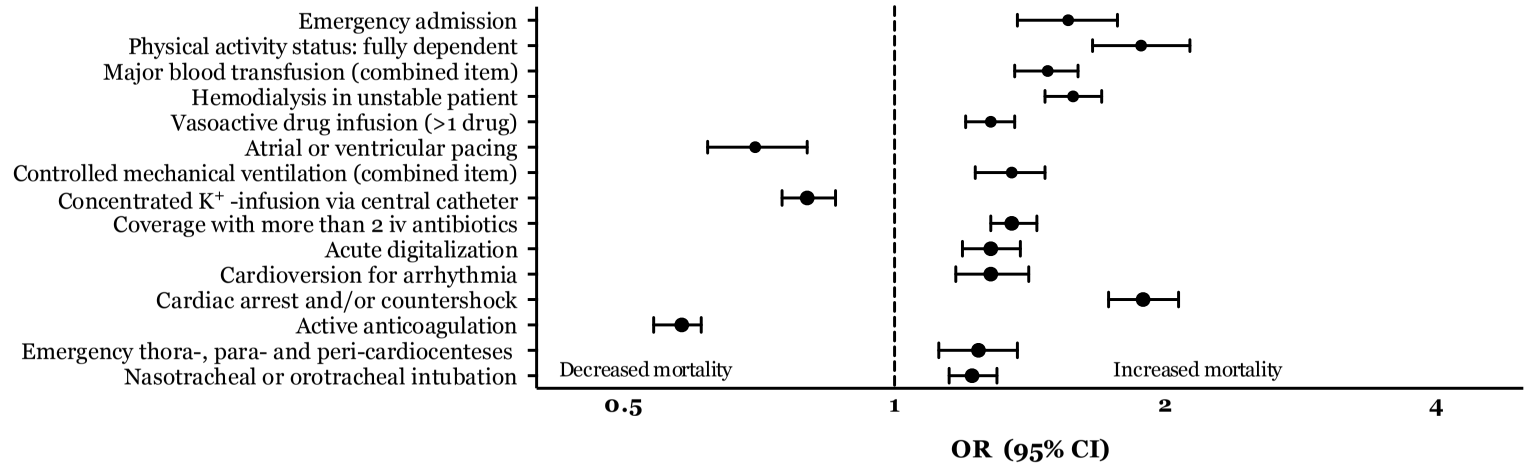

Figure 8. The effect of individual TISS-76 items on the risk of hospital mortality.

TISS, Therapeutic Intervention Scoring System.

Figure reprinted from Efendijev I, Acta Anaesthesiol Scand 2016;60:1415–24 with permission from John Wiley & Sons, Inc.®

6 DISCUSSION

6.1 ICU-CA in the Literature

According to the systematic review of the literature, the patient populations and settings of the published studies were quite heterogeneous. In-hospital Utstein guidelines first appeared in 1997. Thus, most previous studies included in this literature review reported results inconsistently, thereby complicating comparisons, as indicated by the low kappa score. In general, the quality of the reviewed publications was limited, since most of the data on ICU-CA originated from single-centre retrospective studies.

As expected, the time to the initiation of CPR amongst ICU patients was short [18,19]. Most studies also reported time to ROSC, which stood at around 10 minutes for survivors and was noticeably longer for non-survivors. Although delays in the evaluation of the initial rhythm were virtually non-existent, the initial rhythm in the majority of ICU-CAs was non-shockable, indicative of a non-cardiac aetiology. This assumption was supported by the largest ICU-CA study, performed by Tian et al., according to which acute myocardial infarction represented the immediate reason for CA in only 9% of all cases [50].

Aetiology and predisposing clinical conditions also seem to affect ICU-CA outcomes. Circulatory insufficiency before CA served as an apparent aggravating factor, since patients not on vasopressors at the time of arrest exhibited a higher likelihood of survival [50,224]. Furthermore, mortality rates appeared the lowest in post-cardiac surgery patients. In this patient population, CA often associated with a graft malfunction-induced myocardial ischaemia, tamponade or ventricular tachyarrhythmia, all potentially straightforward and treatable clinical conditions given a prompt diagnosis and clear management protocols [118,121]. By contrast, patients from mixed and medical ICUs most likely present more complex CA aetiologies with multiple factors affecting post-ICU-CA survival. For instance, Wallace et al. reported the lowest hospital survival rate in the medical ICU of a comprehensive cancer centre, where only 2% of all ICU-CA patients survived to hospital discharge [20]. Interestingly, ICU-CA incidence (78/1000 ICU admissions) reported in the same study was 5 to 10 times higher than reports from other studies [20,118,122,167,219,226].

Considerable differences in study populations, settings, local CA management and ICU admission policies might represent key factors affecting the observed variability in the ICU-CA incidence. Another, more recent systematic review of the literature and meta-analysis on ICU-CA reported an incidence of ICU-CA of 5 to 78/1000 ICU admissions [227]. That study reports ICU-CA incidence estimates almost identical to the results from study I presented here, despite including a significant number of more recent publications. However, after excluding studies with a high risk of selection bias, the pooled incidence of ICU-CA falls to 15/1000 ICU admissions. This figure is similar to the incidence rates found in study I after excluding the publication by Wallace et al [20].

6.2 Cardiac Arrest Patients in Finland

6.2.1 ICU-CA incidence and survival

Compared to earlier studies, an ICU-CA incidence of 29/1000 in Finnish ICUs appears somewhat high. However, a more recent registry-based study from the US (not included in the systematic review of the literature) reported an ICU-CA incidence of 18/1000, which is also higher than most previously published results [119]. As mentioned above, multiple factors including patient population, ICU admission criteria and DNAR policies can influence ICU-CA incidence. Additionally, the definition of CA adopted in study II may have overestimated ICU-CA incidence since, contrary to previous studies, 'defibrillation only' cases were also included in the analyses. However, ICU-CA incidence at Meilahti Hospital (10/1000 ICU admissions) was similar to earlier reports [227]. The discrepancy in ICU-CA incidence between study II and study IV can be explained by several factors. First, all ICUs at Meilahti Hospital staff on-site physicians experienced in critical care at all times. Furthermore, all major medical specialties are available around the clock. Thus, severely ill and deteriorating ICU patients receive the necessary treatment with minimal delays, whilst potentially futile cases are identified earlier and have DNAR orders sorted prior to further deterioration to CA. Finally, it is also possible that the ICU-CA incidence at Meilahti Hospital was underreported because the cardiosurgical ICU was not a member of FICC at the time of data collection.

Hospital survival (44%) across all Finnish ICU-CA patients was comparable to two recent studies, but was significantly higher than most previous reports [122,167]. Similar hospital survival rates (52%) were also observed among the Meilahti Hospital CA population. Based on the two substudies (II and IV) summarised here, hospital survival amongst Finnish ICU-CA patients was also significantly higher than previously reported hospital survival (5–30%) for IHCA and hospital-treated OHCA patients. ICU patients remain under close and constant surveillance, which in turn leads to shorter delays in the initiation of CPR and, thus, possibly better outcomes. Depending on the institution's DNAR policies, some ICU patients who continue to deteriorate despite adequate maximum organ support and approaching the complete exhaustion of physiological resources may not receive CPR upon acute cardiovascular collapse. Still, it is possible that some ICU-CA cases have an iatrogenic aetiology. These might include profound hypotension or hypoxia due to the overzealous use of sedatives in connection with invasive therapeutic procedures or an acute cardiac arrhythmia during central venous cannulation from guidewire-induced excitation. In such cases, the initiating factor is clear and potentially amenable to treatment. At the same time, full 'combat readiness' amongst ICU staff might lead to the prompt and possibly even proactive initiation of CPR and defibrillation. If a hypothetical ICU combines both features mentioned above, an increased incidence of ICU-CA may arise, simultaneously 'preferring' patients with a better prognosis and withholding CPR from patients with an evident poor outcome, thus improving local ICU-CA survival.

6.2.2 Survival after OHCA and IHCA

Survival rates for OHCA and IHCA patients from Meilahti Hospital were higher compared to previous studies [102,110–114]. The patient population in study IV originates from the Hospital District of Helsinki and Uusimaa. The latter possesses a highly efficient emergency medical system (EMS) and has a high rate of bystander CPR. All patients included in study IV received post-arrest treatment in ICUs from a specialised cardiac arrest centre which staffs experienced intensivists and established post-arrest diagnostic and treatment procedures readily available around the clock. Additionally, study IV included strictly ICU-treated CA patients. Thus, OHCA and non-ICU IHCAs with unsustained ROSC or those denied ICU admission due to a presumed poor outcome were excluded from analysis. Such an approach, in turn, could potentially overestimate survival rates. However, survival for the OHCA population in study IV was comparable to findings reported in earlier Finnish studies on ICU-treated OHCAs [6,109].

6.2.3 Temporal trends in survival

Study II showed that both ICU-CA incidence and mortality have decreased in Finnish ICUs. However, the reason for such a decrease in nationwide ICU-CA incidence and mortality remains unclear. Interestingly, during the study period, the implementation of any type of treatment limitation significantly increased. Additionally, the concept of medical emergency team (MET) was gradually adopted in Finnish hospitals during the study period, which in turn might have resulted in the earlier admission of deteriorating patients to ICUs and the more timely initiation of the appropriate treatment, thereby reducing both ICU-CA incidence and mortality over time. Furthermore, METs may have led to an earlier recognition of futile cases that would not benefit from ICU admission.

In the last decade, numerous publications also reported improvements in short-term survival for OHCA and IHCA [2,3,6,47,54,107,228,229], with at least one study reporting an improved one-year survival for OHCA patients [113]. Such temporal changes might, at least partially, occur due to an overall improvement in the 'chain of survival' [2,113]. However, study IV failed to identify any improvement in the one-year mortality amongst CA patients in the Meilahti Hospital population. Since the American Heart Association introduced the 'chain of survival' concept more widely in 1991, potentially by 2005 (the beginning of study IV), Helsinki's EMS, local CPR training programmes for laypersons and in-hospital post-CA treatment were already quite mature [1]. This could have, in turn, diluted the temporal effect of improved peri-arrest treatment. Relatively high survival rates in the present study's population might reflect this, given that a similar situation was also previously observed in a different population [230].

Study II showed that hospital survival also improved for non-CA patients, suggesting that advancements in medical practices in the past decade, both inside and outside ICUs, might be responsible for the overall better survival of ICU patients generally and CA patients specifically. A more effective initial diagnostic and treatment approach along with the development of systematic treatment protocols could have resulted in better prevention

of the profound deterioration of a patient's condition otherwise resulting in CA. Such practices could potentially reduce both incidence and mortality rates across all CA patients. Simultaneously, medicine continuously gains additional knowledge on the effectiveness and ineffectiveness of certain treatment modalities in selected populations, thus improving clinicians' understanding of specific medical situations, potentially reducing the number of futile efforts and allowing for the redirection of precious resources towards patients most likely to benefit from interventions. The observed increase in the implementation of any type of treatment limitations amongst Finnish ICU patients supports this view. Recently, a large study on ICU-treated CA patients from the UK reported a temporal increase in treatment withdrawal with a concurrent increase in the length of ICU stay, the time to treatment withdrawal and hospital survival rates [231]. The authors of that study suggested that the improved hospital survival of CA patients associates with prolonged ICU treatment and delayed decisions on treatment withdrawal. The nature of the relationship between treatment limitations and ICU-CA patient survival remains unclear. Perhaps, the more active implementation of DNAR orders would reduce ICU-CA incidence as well as ICU-CA mortality. However, the active adoption of DNAR policies should not result in the limitation of other appropriate medical treatments, since such practices that can potentially lead to worse functional outcomes in survivors [232].

6.2.4 Neurological outcomes

Several earlier publications reported prevalence rates for favourable neurological outcomes (CPC 1–2) amongst survivors of between 70% and 90%, rates similar to results from Meilahti Hospital. Notably, the rates for favourable neurological outcomes remained similar irrespective of CA location [48,50,60,109,111,117,122–125]. Such a remarkable similarity across different studies relying on different patient populations from different geographic locations suggests that post-arrest treatment and prognostics practices are also similar. As a result, most CA survivors experience at least a satisfactory neurological and also possibly functional outcome. It is doubtful that such a similarity would occur by chance or simply by redirecting resources to patients perceived as having a better prognosis. Although based on speculation due to the absence of any firm scientific basis, it is possible that international resuscitation guidelines have influenced and unified clinicians' approaches to CA patients. However, it is also important to understand that CPC represents a robust and imprecise tool to assess neurological outcomes, and several studies have indicated that CPC might potentially overestimate positive outcomes [126–129]. Because neurological outcomes continue to improve for many months after CA, it is essential that comparisons between studies take measurements at equivalent time points.

6.2.5 Costs

The total costs reported in study IV consisted of an extensive dataset of direct costs alongside available indirect costs at one year after CA. Due to the lack of reliable data on survivors' quality of life, the effective cost per ICU-treated post-CA survivor served as the

primary tool for the assessment of the economic impact of CA. Owing to the descriptive nature of the study, the aforementioned cost-effectiveness estimates did not require sensitivity analyses [188].

6.2.5.1 Previous studies

Data on CA-related healthcare costs remain scarce. Reported healthcare-associated costs amongst CA survivors vary between €36,000 and €50,000, and between €17,000 and €80,000 (expressed in 2013 euro) for survivors with a favourable neurological outcome [196,198,200,201,233]. Most previous studies included only in-hospital costs or pre- and in-hospital costs combined. Only one study reported post-discharge healthcare-associated costs of €36,600 in 2013 euro per 6-month OHCA survivor [199]. One study also reported ICU costs for ICU-CA hospital non-survivors [20]. Table 15 summarises the detailed characteristics of previous studies on CA-related healthcare costs.

According to previous studies, survival rates were generally lower than those reported here, although amongst ICU-treated CA patients survival rates were similar. Healthcare-associated costs were higher in the present study, yet only one earlier study included data on post-discharge costs [199]. No earlier studies summarised comparable data on ICU-CA costs or the impact of peri-arrest factors on healthcare-associated costs and treatment intensity in ICU-treated CA patients.

Table 15. Summary of studies reporting CA-related healthcare costs

Study	Study year	Study population	Type of costs	Reported costs	Costs in 2013 euro	Hospital survival	Lon-term survival
Jakobsson et al. *Acta Anaesthesiol Scand*	1982	Hospital-treated OHCA	Pre-hospital and in-hospital	US$16,600	€36,000/6-month survivor	32%	29% At 6 months
Næss et al. *Resuscitation*	2000	Hospital-treated OHCA	Pre-hospital and in-hospital	€40,600	€53,000/hospital survivor	25%	16% at 1 year 10% at 5 years 6% at 10 years
van Alem et al. *Circulation*	2001	EMS-treated OHCA	All costs up to 6 months	€29,000	€36,600/6-month survivor	23%	22% at 6 months
Wallace et al. *Support Care Cancer*	2002	ICU-CA	ICU-related costs	US$46,000	€54,000/hospital non-survivors	2%	1% at 6 months
Graf et al. *Crit Care*	2004	ICU-treated OHCA + IHCA	In-hospital	€50,000 €68,000	€60,000/hospital survivor €82,000/5-year survivor	42%	31% at 5 years
Chan et al. *Circ Cardiovasc Qual Outcomes*	2010	IHCA hospital survivors	In-hospital	US$17,980 for CPC 1 US$19,418 for CPC 2	€17,384/hospital survivor CPC 1 €18,774/hospital survivor CPC 2	NR	NR
Petrie et al. *BMJ Open*	2012	ICU-treated OHCA	In-hospital	£51,000 £65,000	€62,000/hospital survivor €79,000/hospital survivor CPC 1–2	48%	NR

CA, cardiac arrest; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; ICU-CA, in-ICU cardiac arrest; EMS, emergency medical service; CPC, Cerebral Performance Category; NR, not reported.

6.2.5.2 Healthcare-associated costs and cardiac arrest location

Notably, IHCA associated with markedly higher total healthcare costs compared to OHCA. This association was even stronger for ICU-CA, a subgroup of the IHCA population that consumes a considerable amount of resources for every survivor, particularly for a survivor with a good neurological outcome. The observed increase in total costs for IHCA and ICU-CA patients primarily resulted from the increase in hospital costs, suggesting that hospital survivors have a similar long-term outcome and, thus, similar post-discharge healthcare utilisation irrespective of the location of the initial CA. Furthermore, in study IV, hospital costs for IHCA and ICU-CA may have included significant pre-arrest expenses, thus overestimating total healthcare costs and particularly hospital costs. However, 67% of all IHCAs in this study experienced CA as early as on the first day of hospital stay.

6.2.5.3 Healthcare-associated costs and initial cardiac rhythm

Asystole as the initial cardiac rhythm associated with a lower treatment intensity, a shorter length of ICU and hospital stays and significantly lower total costs due to the reduced hospital and social security costs. These findings suggest that CA patients with an asystole as initial rhythm might require fewer resources possibly due to the different arrest aetiologies, a higher risk of early mortality and perhaps a presumed poor outcome and less active treatment strategies. In clinical practice, PEA and asystole often receive similar treatment and are considered similar in terms of prognosis. Yet, study IV showed no definitive association between consumed resources and PEA.

6.2.5.4 Healthcare-associated costs, age and severity of illness

An increasing age and higher SAPS II scores associated with lower total healthcare-associated costs, primarily due to lower hospital and social security costs. An inverse association between SAPS II scores and costs emerged when the analyses were repeated only amongst hospital survivors, suggesting an inverse U-shaped relationship between resource consumption and the severity of illness. The more severe the acute illness, the greater the need for resources until the severity of illness increases to a critical level, at which point further increases in the risk of early mortality result in a reduction in resource consumption. Interestingly, age had no influence on treatment intensity or length of ICU and hospital stays, whilst an increase in the SAPS II scores slightly reduced the TISS-76 score and the length of the hospital stay, but exerted no effect on length of ICU stay.

6.2.5.5 Cardiac arrest-related healthcare costs in relation to other critical illnesses

As previously mentioned, in the United States in 2010, critical care medicine consumed US$108 billion or 0.7% of the US GDP [184]. Although the US healthcare system consumes the highest amount of resources in relation to GDP compared to other countries in the world and is not directly indicative of healthcare expenses in Finland, clearly critical care is resource-intensive [184,234]. According to Hamel and colleagues, the treatment costs of

high-risk comatose patients reached US$140,000 per QALY expressed in 1998 US dollars, or €221,000 in 2013 euro [235]. Amongst ICU patients treated for acute renal failure, the mean cost for one 6-month survivor was US$80,000 (expressed in 1993 US dollars), or €117,000 in 2013 euro [236]. The median total cost for a hospital survivor requiring acute renal replacement therapy reached €64,700 in 2013 euro [237]. For critically ill cancer patients, the costs per life gained ranged from US$82,845 to US$189,339 (expressed in US dollars, or €134,000–€305,000 in 2013 euro) [238]. For patients with a traumatic brain injury, the overall effective costs per 1-year survivor and per 1-year independent survivor were US$52,716 and US$83,533, respectively (expressed in 2013 US dollars, or €47,708 and €75,595, respectively, in 2013 euro) [239]. Chin-Yee et al. reported ICU costs for very elderly (≥80 years) patients of CAD$61,783 per 1-year survivor (expressed in 2013 Canadian dollars, or €46,453 in 2013 euro) [240]. Given these figures, the effective cost per one-year survivor with a favourable neurological outcome of €102,722 reported in this study does not seem particularly high, and appears lower than the generally accepted costs of other healthcare interventions [193,194,205]. However, the assessment of costs amongst critically ill patients remains a complex task and comparing studies may be biased by numerous pitfalls [188].

6.3 Association Between Treatment Intensity and Hospital Mortality Amongst Finnish ICU Patients

The creators of TISS initially recommended its use as a measure of the patient's clinical condition [178]. TISS, a continuous activity-based scoring system, enjoys common use in documenting the daily efforts required to care for critically ill patients. The score also indirectly reflects the severity of the illness. Several earlier studies established a relationship between a higher risk for hospital mortality and higher TISS scores as a sign of premature ICU discharge [241–243]. The correlation between higher TISS scores and an unfavourable outcome was also previously noted in different patient populations [244–249]. This association itself seems quite logical, since the more severely ill a patient is the more interventions and resources he or she will consume unless a high early mortality reduces the need for additional resources. Nevertheless, using the TISS score to assess illness severity is complicated, since different units and even different clinicians will apply different thresholds to implement specific supportive therapies. The present study showed that early TISS scores have an additional prognostic value as an early warning sign, particularly amongst patients with an initially low risk of mortality as predicted by conventional severity-of-illness scores. Hence, an activity-based score can bring additional value in the evaluation of mortality risk in settings where activity-based scores are already routinely collected. Yet, collecting activity-based scores can be quite burdensome. Thus, implementing such scores as a prognostic tool is probably not justified if a scoring system is not already in use.

According to the findings presented here, specific TISS items also strongly individually associate with hospital mortality. Amongst these, the strongest association exists for hospital mortality and the TISS-76 item 'cardiac arrest and/or countershock within 48 h', with an effect size similar to a poor preadmission physical status. Whilst CA was not stratified by location in this study, mortality and the incidence of IHCA, and ICU-CA in particular, will likely decrease through the development of more effective early warning and treatment systems both inside and outside ICUs.

7 STUDY LIMITATIONS

The main limitation of the present study lies in its retrospective nature. Studies II through IV are registry-based, and, thus, prone to typical misclassification and misinterpretation biases. Since the majority of ICU-CAs in study II stemmed from the non-operative cardiovascular group, it is possible that OHCA patients with APACHE III admission diagnoses other than CA but with a positive TISS-76 item for CA might have been classified as ICU-CAs. Yet, this is probably quite uncommon in the FICC database due to its multilevel validation process. One should also note that whilst the highest hospital survival rate following ICU-CA emerged in the cardiac surgery population, this study did not include patients from Finland's largest cardiac surgery ICU. The primary outcome of studies II and III lies in the hospital mortality–that is, not an optimal endpoint, given that many patients might be discharged to other hospitals for further care potentially underestimating the mortality rates of the index hospitals. Furthermore, study I included articles published in English only. In addition, due to the significant heterogeneity of the reviewed publications, a quantitative analysis of the data was omitted. In studies II through IV, 2% to 24% of patients had to be excluded due to missing data. Due to the retrospective nature of the study and the limitations of the data sources, separating pre-arrest expenses and resources for IHCA and ICU-CA patients in study IV remained impossible.

It is important to underscore that all relationships between individual variables and patient outcomes should be regarded as merely associative, since the study design and settings did not permit establishing causality between explanatory and dependent variables. Due to the lengthy study period, significant changes in medical practices overall and in CA treatment specifically might have influenced the observed outcomes.

8 CONCLUSIONS

1) The incidence of ICU-CA in Finland appeared somewhat higher than that reported in the earlier literature, possibly due to differences in the definition of CA. Simultaneously, post-ICU-CA mortality appeared markedly lower whilst both incidence and mortality rates decreased during the ten years observed. Furthermore, one-year survival of ICU-treated CA patients generally improved from previous reports, whilst healthcare-associated costs were comparable to previous findings. An in-hospital CA, especially ICU-CA, and PEA associated with significantly higher healthcare costs.

2) An increase in early treatment intensity, expressed as a higher early TISS-76 score, associated with a higher risk of in-hospital death and can be used as an additional warning sign of a patient's deterioration. Furthermore, CA associated with a significant increase in the risk of in-hospital death with an effect-size comparable to a poor preadmission functional status.

9 FUTURE IMPLICATIONS

9.1 In-ICU Cardiac Arrest

Survival following ICU-CA appears better than in earlier reports, thus justifying more active treatment of ICU-CA patients. Furthermore, ICU-CA exhibits certain features that distinguish it from other IHCAs. Despite the existence of in-hospital Utstein guidelines, reporting of ICU-CA still lacks a unified and systematic approach, indicating the need for both additional research and ICU-CA-focused reporting recommendations. Assuming that ICU-CA patients with an iatrogenic arrest aetiology will experience the best prognosis seems reasonable. This rationale, in turn, promotes the more active implementation of prevention strategies for high-risk procedures and patients. Such strategies should include procedural checklists and routine simulation-based training for ICU staff [250,251].

9.2 Early Warning and Treatment Systems

Preventing IHCA through early recognition of deteriorating patients using either dichotomic MET criteria or early warning scores (EWS) serves as the foundation of contemporary rapid response systems [252,253]. The future development of more advanced monitoring systems for general ward patients–that is, continuous wireless monitoring with semi-automated alert systems guided by artificial intelligence–may potentially reduce the incidence of IHCA further. Such systems would allow for the identification of deteriorating ward patients more effectively and timely, helping to prevent CA initially in hospitals and, in the more distant future, possibly even out-of-hospital [254–256]. This could potentially allow clinicians to intervene long before deterioration progresses to the 'point of no return'. However, such systems also require a clear and well-defined DNAR policy. The latter, in turn, remains impossible without a proper understanding of the outcomes acceptable for patients themselves and for society.

9.3 Long-Term Outcomes and Costs

Numerous studies on CA report improvements in post-arrest survival. However, a better survival does not always equate with a better outcome [257]. In order to adequately assess post-CA patient outcomes, it is essential to obtain reliable data on the functional outcome and quality of life. Ideally, clinicians should also consider patients' pre-arrest condition and the grade of disability acceptable for the patient. Post-CA functional outcomes and the quality of life continue to change for at least months after the initial arrest [130,131,258]. Future studies should concentrate on the identification of precise and sensitive tools along with an accurate timing for the optimal assessment of post-CA patient outcomes [259].

More precise knowledge of post-arrest functional outcomes and CA-related healthcare costs might influence societal and medico-professional incentives, resulting in more effective prevention strategies. These strategies might consist of the greater involvement

of laypersons as first responders and improved management and rehabilitation strategies for CA victims. However, it should be stressed that treatment limitations and end-of-life decisions cannot be guided by economic concerns, but should be based on high-quality scientific evidence and valid clinical practice guidelines.

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