SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3466.

NAGY BETTINA

Szív- és érrendszeri betegségek élettana és klinikuma

című program

Programvezető: Dr. Merkely Béla, egyetemi tanár

Témavezető: Dr. Zima Endre, egyetemi tanár

An Integrated Approach to Critically Ill Cardiac Patients: Environmental Risk Factors, Prognostication, and Long-Term Outcomes with Device-Based Follow-Up

Ph.D. thesis

Bettina Nagy, M.D.

Semmelweis University Doctoral School

Cardiovascular Medicine and Research Division

Supervisor: Professor Endre Zima, M.D., Ph.D., M.Sc.

Official reviewers:
Endre Kolossváry, M.D., Ph.D.
Dóra Ujvárosy, M.D., Ph.D.

Head of the Complex Examination Committee: Alán Alpár, M.D., D.Sc.

Members of the Complex Examination Committee:
László Cervenák, M.D., Ph.D.
Mihály Kovács, M.D., Ph.D.

Budapest

2026

Table of Contents

List of Abbreviations

AAD: antiarrhythmic drug

ACS: acute coronary syndrome

AF: atrial fibrillation

AIC: Akaike information criterion

AKI: acute kidney injury

APACHE II: Acute Physiology and Chronic Health Evaluation II

AUC: area under the curve

BLS: basic life support

BMI: body mass index

BP: blood pressure

CABG: coronary artery bypass grafting

CAHP: Cardiac Arrest Hospital Prognosis score

CAD: coronary artery disease

CI: confidence interval

CIED: cardiac implantable electronic device

CNS: central nervous system

COVID-19: coronavirus disease 2019

CPC: cerebral performance categories

CPR: cardiopulmonary resuscitation

CRT: cardiac resynchronization therapy

CRT-D: cardiac resynchronization therapy defibrillator

CRT-P: cardiac resynchronization therapy pacemaker

DLNM: distributed lag non-linear model

ECG: electrocardiography

ECMO: extracorporeal membrane oxygenation

ECPR: extracorporeal cardiopulmonary resuscitation

EEG: electroencephalography

EMS: emergency medical services

HF: heart failure

HR: heart rate

HRV: heart rate variability

ICD: implantable cardioverter-defibrillator

ICU: intensive care unit

IHCA: in-hospital cardiac arrest

IRR: incidence rate ratio

IQR: interquartile range

KCCQ: Kansas City Cardiomyopathy Questionnaire

LV: left ventricle

LVEF: left ventricular ejection fraction

MAP: mean arterial pressure

MOF: multi-organ failure

NSTEMI: non-ST-elevation myocardial infarction

NT-proBNP: N-terminal pro-B-type natriuretic peptide

OHCA: out-of-hospital cardiac arrest

PAD: peripheral arterial disease

PCAC: Pittsburgh Cardiac Arrest Category

PCAS: post-cardiac arrest syndrome

PEA: pulseless electrical activity

RM: remote monitoring

ROC: receiver operating characteristic

ROSC: return of spontaneous circulation

RV: right ventricle

RVEDD: right ventricular end-diastolic diameter

SAPS II: Simplified Acute Physiology Score II

SCA: sudden cardiac arrest

SD: standard deviation

SOFA: Sequential Organ Failure Assessment

SpO_2: peripheral oxygen saturation

STEMI: ST-elevation myocardial infarction

TAPSE: tricuspid annular plane systolic excursion

TIA: transient ischemic attack

TTM: targeted temperature management

VF: ventricular fibrillation

VT: ventricular tachycardia

1. Introduction

1.1. Sudden Cardiac Arrest as a Major Public Health Challenge

Sudden cardiac arrest (SCA) is one of the leading causes of cardiovascular mortality worldwide and despite substantial advances in diagnostic and therapeutic options, it is still associated with an unfavorable prognosis (1, 2, 3). According to the most widely accepted definition, SCA is considered a natural, unexpected death occurring within one hour from symptom onset or in the absence of witnesses, it is defined as death in an individual who was seen alive and symptom-free within the preceding 24 hours (1).

Based on the location of the event, cardiac arrest can be classified as out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA). From both clinical and public health perspectives, OHCA is of particular importance, as the vast majority of cases occur unexpectedly outside the healthcare system, and survival rates remain low even with optimal medical care and early reactions (4, 5, 6).

The present dissertation primarily focuses on out-of-hospital cardiac arrest; therefore, this condition is discussed in detail in the following sections before addressing the long-term management of high-risk cardiac patients. The epidemiology of OHCA in Europe is most comprehensively characterized by the latest data from the European Registry of Cardiac Arrest (EuReCa III), which analyzed more than forty thousand cases (7). According to this registry, the incidence of confirmed OHCA in Europe was 82.3 cases per 100,000 population per year, while the incidence of Emergency Medical Services (EMS) treated OHCA was 55.6 per 100,000 population per year, with substantial inter-country variability depending on registry methodology and case definition (7).

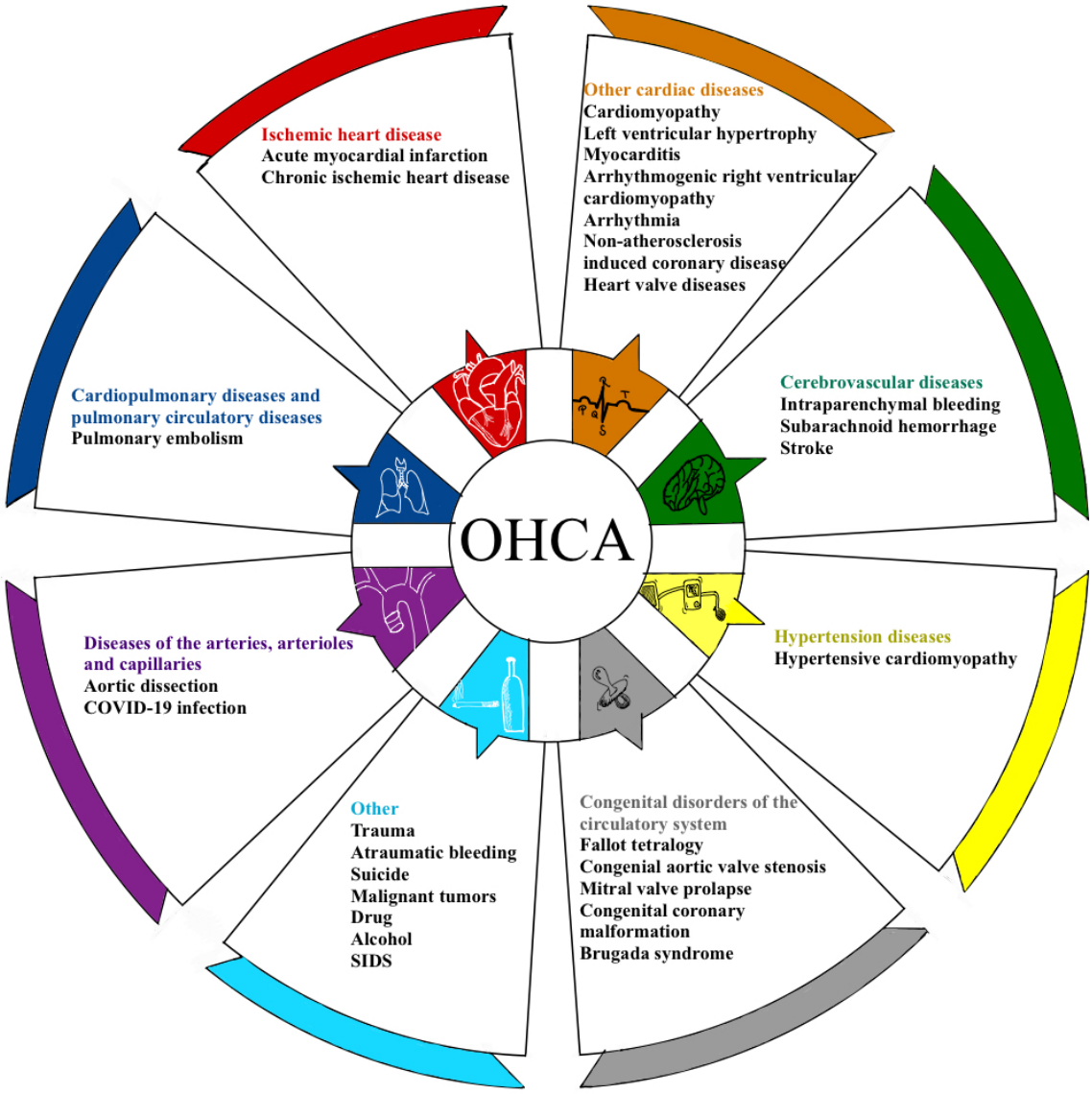


Figure 1: The most common causes of OHCA (own flowchart) (Source: Nagy B, Kiss B, Fülöp GÁ, Zima E. Out-of-Hospital Cardiac Arrest in General Population and Sudden Cardiac Death in Athletes. IntechOpen. 2022. doi:10.5772/intechopen.101813. CC BY 4.0) (8).

Abbreviations: COVID-19: coronavirus disease 2019; SIDS: sudden infant death syndrome

Figure 1 provides an overview of the main etiological categories of OHCA (8). The etiological spectrum of SCA is dominated by cardiac causes, including ischemic heart disease, cardiomyopathies, and primary electrical disorders; however, a substantial proportion of events arise from non-cardiac triggers (9, 10). These include massive pulmonary embolism, severe hypoxia or asphyxia, traumatic or non-traumatic major hemorrhage, aortic rupture, severe electrolyte disturbances, intoxication with drugs or medication overdose, and acute cerebrovascular events such as subarachnoid hemorrhage (8). In such cases, cardiac arrest develops as a consequence of an acute, life-threatening

dysfunction of another organ system, which secondarily leads to circulatory collapse and loss of effective cardiac pump function (11, 12).

OHCA events occur significantly more frequently in males, who account for 65% of cases according to the EuReCa III trial, while incidence rises with advancing age, with a mean patient age of 67.6 ± 17.5 years (7). In EMS treated cases, the return of spontaneous circulation (ROSC) rate is 32.3% on average, and sustained spontaneous circulation on hospital arrival is achieved in approximately 25% of cases (7).

Despite successful resuscitation, early mortality remains substantial, and although the majority of survivors discharged from hospital leave with a favorable neurological status, representing only a low ratio of all OHCA cases (7, 13). Overall survival to hospital discharge is approximately 7-10% across Europe, with considerable variability between countries (7).

The most recent European Resuscitation Council (ERC) guidelines published in 2025 emphasize that SCA is not a distinct disease entity but rather a final common pathway resulting from various cardiovascular and non-cardiovascular pathological processes (13). According to the guidelines, both the occurrence of the event and its outcome are jointly determined by the patient's individual vulnerability, including genetic predisposition and underlying structural and functional cardiac abnormalities, triggering environmental and physiological influences, as well as the quality of acute resuscitation care and post-resuscitation management (13).

Accordingly, a contemporary approach to SCA requires an integrated perspective that spans from the identification of population-level risk factors through acute intensive care management to the long-term follow-up of survivors. The 2025 ERC guidelines place particular emphasis on the role of standardized, registry-based data collection and system-level interventions in improving survival outcomes (13).

1.2. The Multilevel Nature of Sudden Cardiac Arrest

In the following sections, SCA is interpreted as a dynamic process in which population-level risk factors, acute resuscitation and intensive care management, and the long-term follow-up of survivors interact in a sequential and interdependent manner to determine

outcomes. The three publications forming the basis of this dissertation each address one of these key stages in the continuum of sudden cardiac arrest care.

At the population level, the risk of SCA is known to be jointly influenced by demographic characteristics, comorbidities, and environmental exposures (10, 14, 15, 16). In addition to age, sex, and pre-existing cardiovascular disease, environmental factors become particularly relevant in situations where they impose acute physiological stress on an already vulnerable population (17).

Ambient temperature has been identified as an important environmental stressor affecting cardiovascular stability. Acute exposure to extreme cold or heat may precipitate hemodynamic, autonomic, and electrophysiological disturbances, and epidemiological studies have consistently linked such conditions to an increased incidence of out-of-hospital cardiac arrest, especially in high-risk populations (18, 19). In recent years, this relationship has been examined in the context of climate change, focusing on the cardiovascular effects of changing temperature patterns at the population level (20, 21, 22).

Following the occurrence of the event, the quality of acute care determines short-term survival. Early and effective resuscitation, achievement of ROSC, and subsequent intensive care after hospital admission represent interrelated components that together influence prognosis (23, 24). Nevertheless, early mortality remains substantial even after successful resuscitation, which is primarily explained by the complex pathophysiology of post-cardiac arrest syndrome developing after circulatory arrest (25).

The central components of post-cardiac arrest syndrome (PCAS) include hypoxic-ischemic brain injury, reversible myocardial dysfunction, and the systemic ischemia-reperfusion response with inflammatory activation, which together contribute to early organ failure and adverse outcomes (24, 26). International guidelines therefore consider post-resuscitation care to be one of the key determinants of survival and neurological outcome (13).

Even after successful resuscitation, the consequences of SCA extend beyond the acute phase of care. Cellular injury resulting from global ischemia and subsequent reperfusion frequently leads to reversible or persistent myocardial dysfunction, which may manifest

as a reduction in left ventricular ejection fraction (27). Therefore, pre-existing heart failure may progress more rapidly, or de novo heart failure may develop during the post-resuscitation period even in patients with previously structurally normal hearts (27, 28, 29).

Following myocardial injury, structural and electrical remodeling may persist, leaving survivors at an increased risk of recurrent malignant ventricular arrhythmias. This elevated arrhythmic risk constitutes an important mechanism underlying recurrent SCA and has been documented in observational cohorts with long-term follow-up (30, 31).

Because of these causal relationships, the long-term management of patients who survive SCA aims not only to optimize heart failure therapy but also to prevent recurrent SCA through secondary prevention strategies. As part of this strategy, and in the presence of appropriate clinical and functional criteria, device-based therapy may be indicated, including implantable cardioverter-defibrillator (ICD) therapy or cardiac resynchronization therapy (CRT) (1). These interventions have been shown to reduce the incidence of recurrent life-threatening ventricular arrhythmias and late mortality, thereby improving long-term survival and quality of life (1, 24).

Based on these considerations, the care of patients who survive sudden cardiac arrest requires structured cardiology follow-up, as the timely recognition and targeted management of post-resuscitation complications directly influence long-term clinical outcomes (6, 24).

1.3. The Physiological and Pathophysiological Role of Temperature Exposures in Out-of-Hospital Cardiac Arrest

Extreme temperatures profoundly impact cardiovascular function by necessitating substantial physiological adaptations, primarily through alterations in peripheral circulation, blood pressure regulation, heart rate, and autonomic nervous system balance (32). In healthy individuals, these compensatory responses maintain homeostasis effectively; however, patients with reduced cardiovascular reserve often exhibit maladaptive reactions that precipitate pathological outcomes (17, 33).

During cold exposure, sympathetic nervous system activation triggers peripheral vasoconstriction, elevating systemic vascular resistance and blood pressure.

Concurrently, cardiac workload and myocardial oxygen demand increase, potentially precipitating ischemia and electrophysiological instability, while cold-induced hemoconcentration and elevated blood viscosity further heighten thrombotic and arrhythmic risks (17, 18, 21).

During heat exposure, peripheral vasodilation develops to facilitate heat dissipation, reducing central circulating volume and blood pressure, while heart rate increases to maintain cardiac output. Fluid loss and disturbances in electrolyte balance further compromise hemodynamic stability and may promote the development of cardiac arrhythmias. Heat stress may also disrupt autonomic nervous system regulation, leading to increased electrophysiological vulnerability (17, 34).

These physiological effects do not act in isolation but may accumulate on the background of pre-existing structural or functional heart disease. Temperature exposure should therefore be interpreted not as an independent etiological factor, but rather as an acute triggering mechanism that, through disruption of cardiovascular homeostasis, may contribute to the development of malignant arrhythmias and circulatory collapse.

1.4. Epidemiological Investigation of the Association between Temperature Exposure and Out-of-Hospital Cardiac Arrest

The relationship between temperature exposure and OHCA has been examined primarily through population-based epidemiological studies, given that the event is rare, sudden, and difficult to predict at the individual level. Most published studies to date have applied time-series or case-crossover designs, which are well suited to evaluating short-term environmental exposures in relation to acute cardiovascular events in large populations (21, 35).

These studies have generally reported an association between extreme temperature conditions and the incidence of OHCA; however, the direction, magnitude, and temporal pattern of the effect have not been uniform. Some investigations have primarily highlighted increased risk related to extreme cold, whereas others have emphasized the impact of extreme heat (35). In addition, differences have been observed regarding whether the effect occurs immediately or manifests with a delay of several days (18, 36, 37).

In recent years, increasing attention has been directed toward the joint evaluation of non-linear associations and delayed effects, as several studies suggest that the relationship between ambient temperature and OHCA cannot be adequately described by simple linear models. In a Korean cohort, the association between ambient temperature and OHCA incidence followed a J-shaped pattern, with heatwave conditions being associated with a marked increase in risk (38). Similarly, a Japanese case-crossover study reported increased OHCA risk at both high and low temperature ranges, further supporting a non-linear exposure-response relationship (39). In addition, multicenter studies indicate that the association between non-optimal temperature ranges and OHCA risk varies across geographic regions, both in magnitude and temporal pattern, likely reflecting climatic differences and population-specific vulnerability (20).

The comparability of international findings is further challenged by heterogeneous definitions of temperature exposure, methodological differences in exposure assessment, and population-specific climatic and health characteristics. All together, these factors contribute to variability in risk estimates and underscore the need for region-specific analyses using standardized methodology, particularly within large European registry-based datasets (7, 21).

1.5. The Significance of Temperature Exposures in the Carpathian Basin

The relationship between ambient temperature and OHCA has been examined across multiple geographic regions over the past two decades. Large population-based studies from North America, Western Europe, and East Asia consistently indicate that both extreme cold and sustained high temperatures are associated with an increased risk of cardiovascular events, including OHCA (37, 39, 40).

From a climatic perspective, the Carpathian Basin represents a transitional zone in which a sustained increase in ambient temperature and a gradual shift in temperature patterns have been consistently documented over recent decades (41). In parallel, the frequency and characteristics of both heatwaves and cold spells have changed in the region, potentially altering the timing and intensity of temperature-related exposure in the general population (42).

Figure 2 illustrates the spatial distribution of climate zones in Hungary according to Péczely's classification for the 1991-2020 reference period, which represents the most recent standardized climatological dataset available (43). This classification highlights the regional heterogeneity of climatic conditions within the country and provides essential contextual information for the interpretation of temperature-related effects examined in the present work.

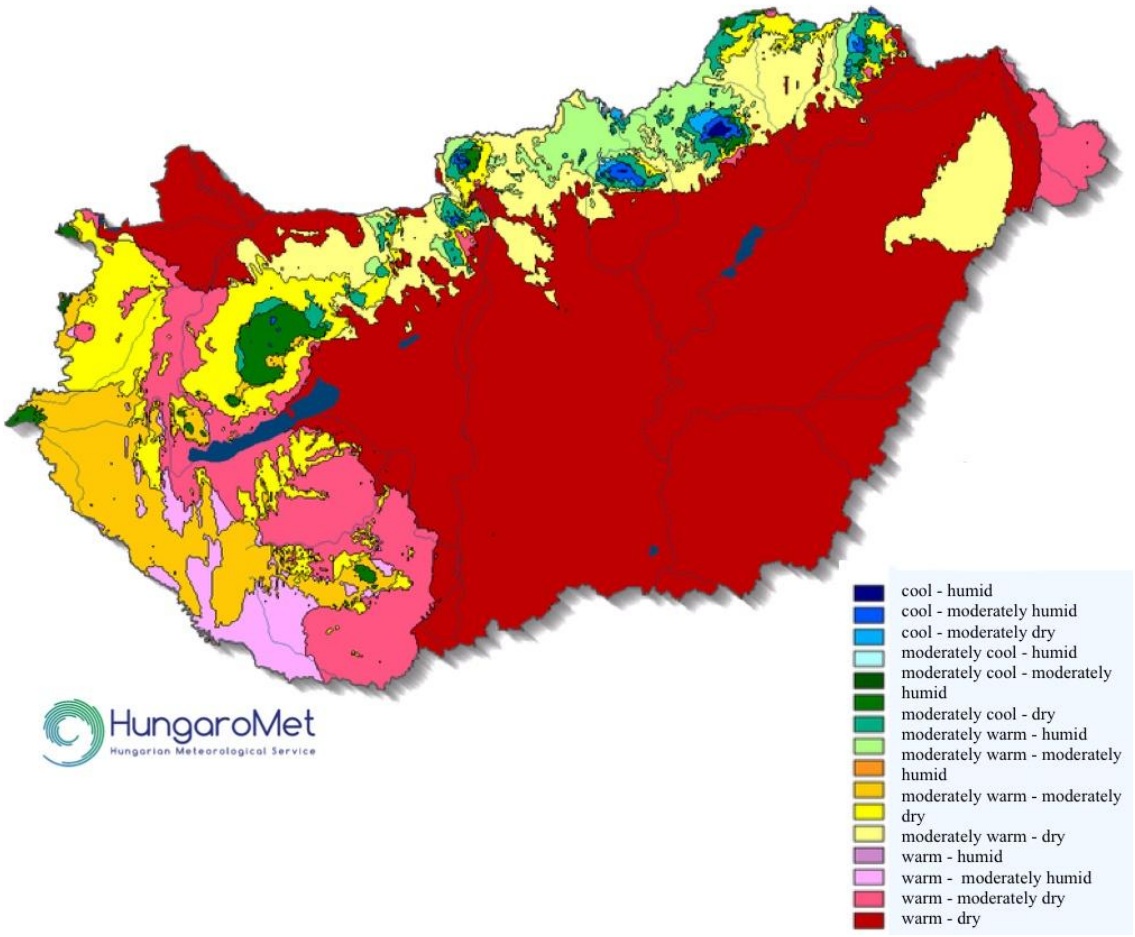


Figure 2. Hungary's climate zones in the period 1991-2020 based on Péczely's classification (43)

In populations with a high cardiovascular risk burden, altered temperature exposure may act as a clinically relevant acute trigger for cardiac arrest. However, international studies have shown substantial geographic variability in both the magnitude and temporal characteristics of the association between ambient temperature and OHCA incidence (35). Large-scale, population-based analyses focusing specifically on the Carpathian Basin remain limited, which underscores the need for region-specific investigations in the context of recently changing temperature patterns (7).

While population-level vulnerability factors are critical for understanding and preventing OHCA, early outcome among survivors is primarily determined by post-resuscitation pathophysiology and acute intensive care management.

1.6. Post-Cardiac Arrest Syndrome and Challenges of Intensive Care

Following the ROSC, PCAS represents the most important determinant of early mortality and morbidity. The pathophysiological components of the syndrome include hypoxic-ischemic brain injury resulting from the no-flow and low-flow phases of cardiac arrest, transient myocardial dysfunction, a systemic inflammatory response resulting from ischemia-reperfusion injury, as well as the persistent effects of the underlying disease or triggering cause (24, 44, 45).

Hypoxic-ischemic brain injury is a key determinant of outcome (45). Following global cerebral ischemia, secondary injury mechanisms are activated during reperfusion, leading to progressive neuronal damage through excitotoxicity, oxidative stress, mitochondrial dysfunction, and neuroinflammation. The clinical manifestations of these processes are reflected in early neurological injury and, subsequently, in unfavorable long-term functional outcomes (46).

Post-resuscitation myocardial dysfunction most commonly presents as global left ventricular systolic impairment and may cause significant hemodynamic instability in the early phase of intensive care. Although this condition is often reversible within 48-72 hours, severe forms may progress to cardiogenic shock, requiring invasive monitoring and targeted invasive hemodynamic support (29).

The systemic inflammatory response triggered by ischemia-reperfusion may involve multiple organ systems and often results in a sepsis-like clinical presentation. The interplay of neurological, cardiac, and systemic processes creates a dynamically evolving clinical state in which the early timing of intensive care interventions plays a critical role (24, 45).

Targeted temperature management has remained a cornerstone of post-cardiac arrest care. However, its conceptual framework has evolved substantially in recent years. According to the latest ERC guidelines, active prevention of fever and maintenance of controlled normothermia are recommended in comatose patients admitted to intensive care

following ROSC, while the routine use of mild or deep hypothermia is no longer advised. The therapeutic goal is to maintain body temperature at maximum of 37.5 °C for at least 72 hours, with particular emphasis on the early detection and treatment of fever (24, 44, 45).

This paradigm shift underscores that temperature management is not an isolated therapeutic intervention, but rather an integral component of comprehensive post-resuscitation care. Its effectiveness depends on the patient's individual vulnerability, the severity of hypoxic-ischemic brain injury, and its integration with other elements of intensive care management.

The phases of cardiac arrest and PCAS, alongside their associated mechanisms, clinical manifestations, therapeutic interventions, and approaches to prognostic assessment, are summarized in Figure 3 (47).

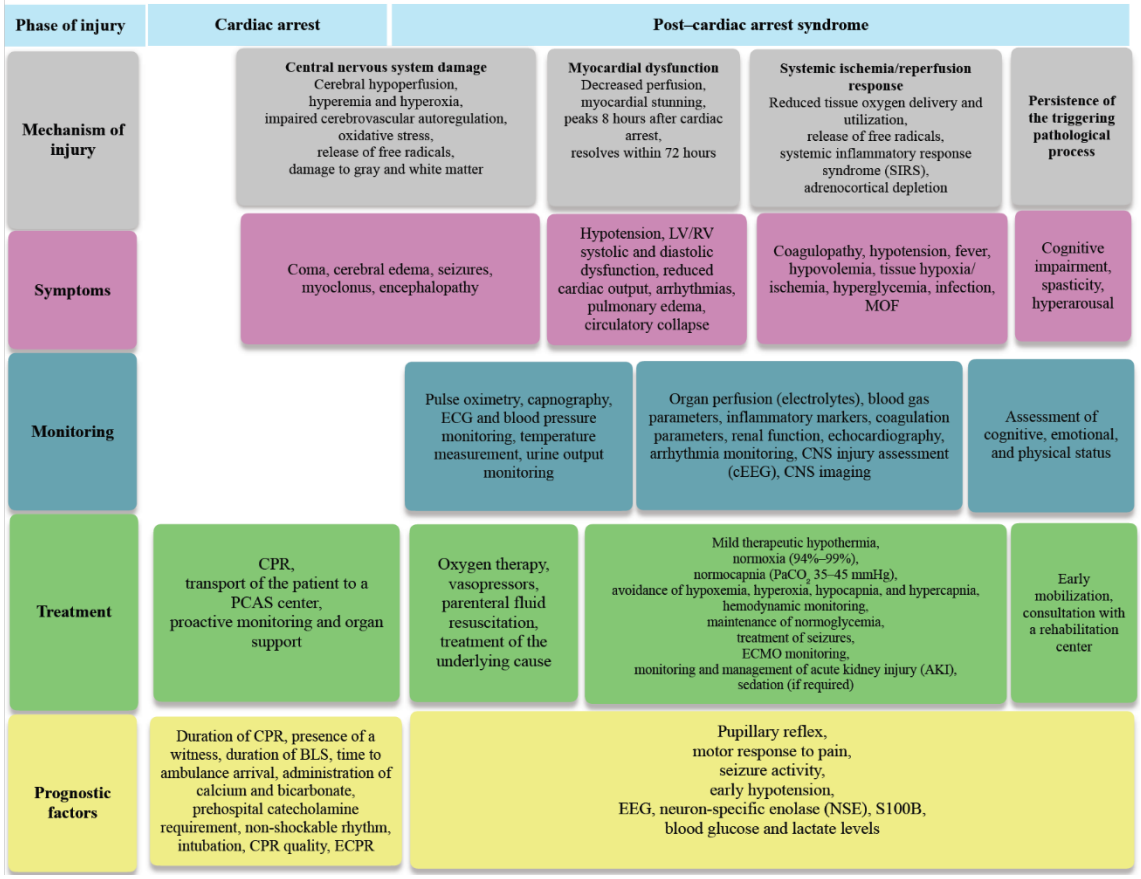


Figure 3. Phases of cardiac arrest and post-cardiac arrest syndrome (PCAS) with the associated pathophysiological mechanisms, clinical manifestations, therapeutic interventions, and prognostic factors (own illustration) (47).

Abbreviations: AKI, acute kidney injury; BLS, basic life support; CNS, central nervous system; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; EEG, electroencephalography; ECG, electrocardiography; LV/RV, left ventricle/right ventricle; MOF, multi-organ failure; PCAS, post-cardiac arrest syndrome.

1.6.1. Targeted Temperature Management

Temperature control is one of the most important neuroprotective interventions in post-cardiac arrest care; however, the approach to its application has changed substantially in the recent years. Early studies suggested a survival and neurological benefit of therapeutic hypothermia in the range of 32-34 °C (48). In contrast, the large randomized TTM2 trial (Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest) did not demonstrate a significant difference between deep hypothermia and controlled normothermia with respect to either mortality or neurological outcome (48, 49). However, the TTM2 population was relatively favorable, with short no-flow times, high rates of bystander CPR, and a predominance of shockable rhythms, which may have limited the severity of hypoxic-ischemic brain injury and reduced the potential observable

benefit of deeper hypothermia. Consequently, the results may not be fully generalizable to higher-risk subgroups (e.g., prolonged no-flow/low-flow time, non-shockable rhythms, or more severe hypoxic-ischemic encephalopathy), although current evidence still supports guideline-based targeted normothermia as the standard approach (49).

Accordingly, the most recent European recommendations emphasize the active prevention of fever and the maintenance of controlled normothermia in post-resuscitation care, particularly in patients who remain comatose (50, 51). Routine application of deep hypothermia in all patients is not recommended. At the same time, the guidelines underline that individualized use of temperature management, implemented as part of an institutional protocol, may still be considered in selected patients with suspected severe hypoxic-ischemic brain injury (52).

This approach is consistent with clinical practice in which temperature control is not treated as an isolated therapeutic target, but rather as a modulating component of comprehensive PCAS care, closely integrated with neurological status, hemodynamic stability, and other intensive care interventions.

1.6.2. The Cooling Process

The steps of targeted temperature management (TTM) are illustrated in Figure 4. Prior to initiation of cooling, documentation of baseline core temperature, airway protection, initiation of mechanical ventilation, achievement and maintenance of adequate sedation, and administration of neuromuscular blockade are essential. The cooling process can be divided into three phases. During the induction phase, the goal is to reduce core body temperature as rapidly as possible. In the maintenance phase, the target temperature typically within the range of 32-36 °C should be maintained. This is followed by the rewarming phase, which must be performed gradually, at a rate not exceeding 0.25-0.5 °C per hour. After normothermia is achieved, the development of fever should be strictly

avoided, as each degree increase above 37 °C is associated with a higher risk of poor neurological outcome (53).

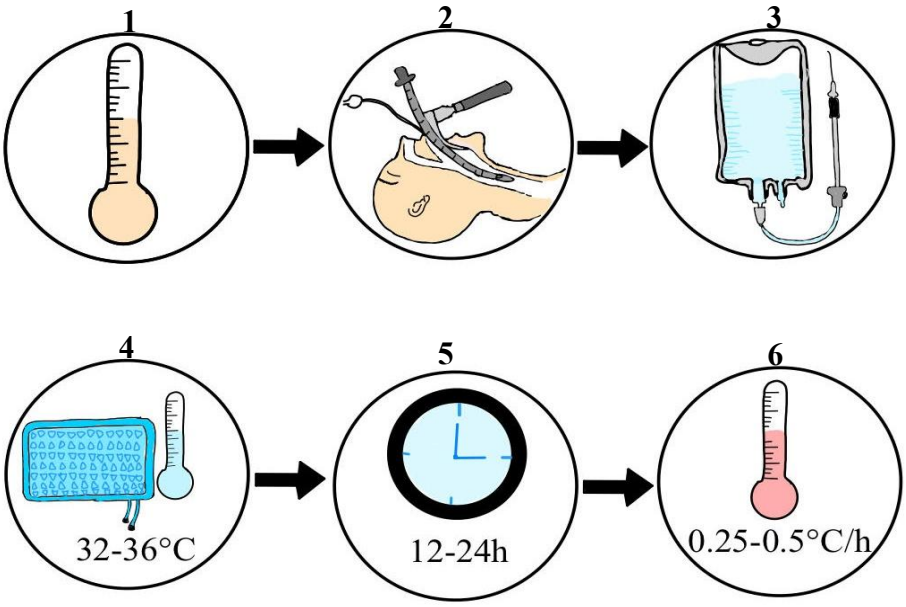


Figure 4. Steps of targeted temperature management (own illustration)

1. Core body temperature measurement,
2. airway protection and mechanical ventilation,
3. administration of sedatives and neuromuscular blocking agents,
4. induction phase of cooling,
5. maintenance phase,
6. rewarming phase.

1.6.2.1. Timing and Methods of Targeted Temperature Management

The extent of hypoxic brain injury is largely determined by the duration of ischemia or anoxia. After approximately five minutes, cerebral ATP and glucose stores become depleted; therefore, this time point is generally considered the limit of anoxia tolerance. Several studies have shown that earlier initiation of cooling is associated with more favorable outcomes; however, even when therapeutic hypothermia is started up to 8 hours after the ROSC, a lower incidence of hypoxic brain injury has been observed compared with control groups (46, 54, 55). These findings support the initiation of hypothermia as early as possible.

Cooling techniques can be broadly divided into external and internal methods. External surface cooling methods are based on heat exchange at the body surface and include cooling blankets, evaporative cooling devices, and automated systems that circulate temperature-controlled fluids (56, 57, 58).

The Blanketrol® system (manufacturer: Cincinnati SubZero Medical Division, Cincinnati, Ohio, USA) consists of a control unit, a compressor, a circulating pump, and blankets or pads (Figure 5). The device pumps warmed or cooled distilled water through the blanket, which is positioned over regions with large superficial vessels (inguinal, subclavian, and cervical areas) as well as the abdominal wall. The water circulates within the blanket and then returns to the device. Pre-programmed temperature gradients in both cooling and warming modes allow sufficiently rapid, gradual, and safe regulation of body temperature. The effectiveness of cooling should be continuously monitored using a core temperature probe placed in the esophagus. Naturally, several other commercially available surface cooling systems based on similar principles are also in use (e.g., Arctic Sun®).

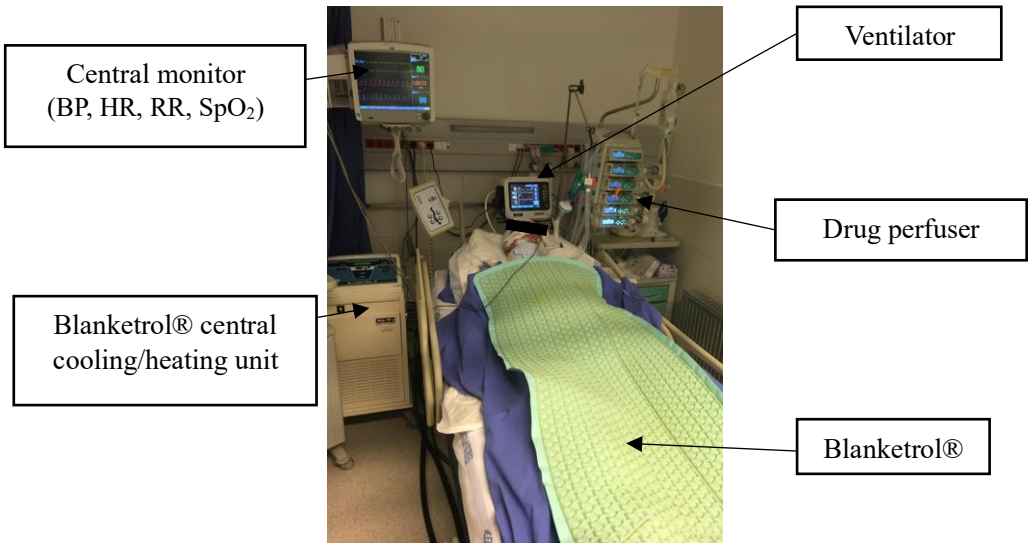


Figure 5. Blanketrol® surface temperature management system based on surface heat exchange, used at the Semmelweis University Heart and Vascular Center, and its main components (own illustration)

Abbreviations: BP, blood pressure; HR, heart rate; RR, respiratory rate; SpO_2, oxygen saturation.

The other major group includes cold intravenous infusions, cold-water gastric or bladder lavage, and intravascular cooling catheters, which enable internal cooling (56, 57). Overall, both endovascular cooling systems and devices based on surface heat exchange

provide faster induction of hypothermia and more effective temperature maintenance than conventional surface cooling methods. Automated systems are also capable of controlled, gradual rewarming, thereby facilitating the prevention and management of post-hypothermia fever. Their main limitation is higher cost (59).

Hypothermia can be classified into different levels: mild (32-35 °C), moderate (29-31 °C), and deep (<28 °C). In the context of mild therapeutic hypothermia, reliable continuous temperature monitoring and strict temperature control with minimal fluctuations are essential. It should be taken into account that brain temperature may differ from systemic temperature by approximately 0.1-0.2 °C (60). Several methods are available for core temperature monitoring, most commonly intravascular, esophageal, transurethral, or rectal probes. Surface body temperature measurements are not suitable for monitoring therapeutic hypothermia (53).

1.6.2.2. Rewarming

After therapeutic hypothermia, a gradual increase in core body temperature of 0.25-0.5 °C per hour is recommended. Rapid rewarming significantly increases the risk of complications, including hypoglycemia, hyperkalemia, and hypotension caused by vasodilation (61). In such cases, intravenous fluid infusion may be useful to maintain mean arterial pressure. After normothermia has been achieved, the primary goal is to prevent the development of fever. If fever occurs, the target temperature should be reset to 36 °C when automated cooling is used, whereas with conventional cooling methods antipyretic pharmacological therapy or physical cooling measures may be required (62).

1.6.3. The Role of Early Risk Assessment in the Cardiac Intensive Care Unit

In patients with PCAS, early prognostic assessment is challenging, while the most critical therapeutic decisions are often made within the first hours after ROSC. Neurological examination is frequently confounded by sedation and temperature management, hemodynamic and organ function parameters may change rapidly; therefore, clinical judgment should be complemented by objective risk stratification tools (63).

Several scoring systems and prediction models have been proposed in the literature to estimate outcomes of post-cardiac arrest patients, particularly in populations treated with

TTM (Table 1). General intensive care unit scores developed for specific intensive care unit (ICU) patient population outcomes, such as APACHE II, SAPS II, or SOFA, have shown only moderate discriminatory performance in this specific TTM patient group in multiple studies (64, 65). In contrast, several models developed specifically for use after cardiac arrest, including CAHP, rCAST, PCAC, MIRACLE2, and the TTM risk score, have generally demonstrated good predictive performance, with area under the curve values exceeding 0.80 in several cohorts (66, 67, 68, 69, 70, 71, 72).

However, the clinical applicability of these models is heterogeneous, as they differ in timing of calculation, required clinical variables, and the populations in which they were developed, and their practical difficulty in daily clinical use. This underscores the need for early, post-cardiac arrest-specific, and easily applicable risk assessment tools that rely on routinely and rapidly available intensive care parameters and can support early clinical decision-making, including the individualization of temperature management strategies.

Table 1. ROC-based comparison of different scoring systems and models for prognostication in patients with PCAS undergoing TTM (source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0).

Abbreviations: APACHE II: acute physiology and chronic health evaluation II; CAHP: cardiac arrest hospital prognosis; OHCA: out-of-hospital cardiac arrest; PCAC: Pittsburgh Cardiac Arrest Category; rCAST: revised cardiac arrest survival test; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment; TTM: targeted temperature management

First author	Year	Study design		Study period	Country	No. of patients	PCAS after	No. of TTM patients (%)	Mortality outcome	Prediction model or score system	AUC
Chen CH (66)	2022	retrospective cohort	single center	2015-2021	Taiwan	108	OHCA or IHCA	108 (100)	28-day mortality	rCAST	0.794 (0.706-0.866)
Lim HJ (73)	2022	observational study	multi center	2016-2020	Korea	4712	OHCA	531 (11.3)	favorable neurological outcome, survival to hospital discharge	ED-PLANN	Development cohort: 0.93 (95% CI, 0.92-0.94) Validation cohort:0.94 (95% CI, 0.92-0.95)
Pareek N (72)	2020	prospective cohort	single center	2012-2017	United Kingdom	373	OHCA	NA	poor neurological outcome	MIRACLE2	Development cohort: 0.90, validation cohorts: 0.84/0.91
Matsuda J (64)	2020	retrospective cohort	single center	2015-2018	Japan	231	OHCA	144 (62)	30-day mortality	SOFA	0.852 (0.803-0.900)

First author	Year	Study design		Study period	Country	No. of patients	PCAS after	No. of TTM patients (%)	Mortality outcome	Prediction model or score system	AUC
Nishikimi M (69)	2019	prospective cohort	multi center	2014-2015	Japan	460	OHCA	460 (100)	30- and 90-day mortality	rCAST	0.832
Isenschmid C (68)	2018	prospective cohort	single center	2012-2017	Switzerland	349	OHCA or unobserved IHCA	200 (57)	in-hospital and 30-day mortality	CAHP, OHCA, APACHE II, SAPS II	OHCA: 0.80 (0.75, 0.85); CHAP: 0.85 (0.80, 0.89); APACHE II: 0.80 (0.75, 0.84); SAPS II: 0.78 (0.73, 0.83)
Yoon JC (65)	2018	retrospective cohort	single center	2010-2015	South Korea	143	OHCA	143 (100)	28-day mortality	SOFA, APACHE II	At admission: SOFA: 0.634 (0.541-0.726); extracerebral SOFA: 0.619 (0.525-0.713); APACHE II: 0.637 (0.546-0.729)
Choi JY (67)	2018	retrospective cohort	single center	2010-2013	South Korea	173	OHCA	173 (100)	30-day mortality	APACHE II, SAPS II, OHCA	At 0 h: APACHE II: 0.715 (0.642-0.781); SAPS II: 0.686 (0.612-0.755); SOFA: 0.641 (0.564-0.712); OHCA: 0.740 (0.668-0.805)
Martinell L. (74)	2017	post hoc analysis	multi center	2010-2013	Europe and Australia	933	OHCA	939 (100)	6 months survival	Target temperature management risk score	0.842 (0.840-0.845)
Coppler PJ (71)	2015	prospective and retrospective cohort	multi center	2011-2013	United States	607	OHCA and IHCA	420 (69.2)	survival to hospital discharge	PCAC	0.82
Maupain C (70)	2015	prospective cohort	multi center	2011-2012	France	819	OHCA	NA	neurological status at ICU discharge	CAHP	Development cohort: 0.93, Validation data sets: 0.91 and 0.85

1.7. Long-term Cardiovascular Consequences and Device-Based Follow-Up in High-Risk Cardiac Patients

After survival from OHCA, the clinical course rarely ends with discharge from the intensive care unit, as the underlying disease and organ injuries related to the arrest continue to influence long-term morbidity and mortality (75, 76). A key issue in long-term management is whether the patient had pre-existing structural heart disease and heart failure, or whether a new, persistent left ventricular dysfunction develops in the post-arrest period, as these scenarios imply different clinical trajectories and distinct therapeutic priorities (75, 77).

1.7.1. Heart Failure, Arrhythmia Prevention, and Device Therapy in High-Risk Cardiac Patients

In a substantial proportion of SCA survivors, an underlying structural heart disease is present or subsequently identified. Accordingly, a cornerstone of post-arrest care is the exclusion of reversible causes and the targeted treatment of the underlying condition, with particular attention to left ventricular function and the risk of progressive heart failure (1, 61, 76, 78). In addition, in patients with persistent left ventricular dysfunction and high arrhythmic risk who have not experienced a documented malignant ventricular arrhythmia, device-based therapy may be considered for primary prevention in accordance with current guideline recommendations (1). In patients who have experienced documented ventricular fibrillation or hemodynamically unstable ventricular tachycardia without a clearly reversible trigger, implantable cardioverter-defibrillator therapy is fundamental for secondary prevention, as it effectively reduces mortality related to recurrent malignant ventricular arrhythmias (1).

From a heart failure perspective, two typical clinical trajectories can be distinguished after survival from OHCA. In patients with pre-existing heart failure, disease progression and recurrent episodes of decompensation are common, whereas in those without previously known heart disease, arrest-related myocardial injury together with subsequently diagnosed cardiomyopathy may lead to persistent functional deterioration (75, 78). In the presence of sustained, clinically relevant left ventricular dysfunction and appropriate QRS and electrical criteria, cardiac resynchronization therapy may represent an important option to improve prognosis and symptoms. Therefore, device-based stratification should follow contemporary pacing and CRT guidelines and be embedded in a structured long-term follow-up strategy (79).

1.7.2. Remote Monitoring and Follow-up in High-Risk Cardiac Patients

Remote monitoring plays an increasingly important role in the follow-up of patients with heart failure living with cardiac implantable electronic devices (CIEDs). Device-based, multi-parametric telemonitoring enables the early detection of arrhythmias, device-related issues, and changes related to patient activity and indirect information of heart failure status, thereby supporting timely clinical intervention.

The clinical benefit of telemonitoring was first demonstrated in a randomized setting by the IN-TIME trial, in which multi-parametric remote monitoring was associated with a significant reduction in mortality among heart failure patients with CIEDs (80). These findings provided the basis for the incorporation of telemonitoring into guideline-level recommendations (81).

The expansion of indication criteria and the widespread availability of devices over the past decade have led to a substantial increase in the number of implantations. Between 2017 and 2020, nearly 4,000 ICD and approximately 4,100 CRT implantations were performed in Hungary (82). In parallel with the growing number of patients living with CIEDs, the burden of patient follow-up has also increased (82).

In Hungary, the first follow-up visit is typically scheduled one week after implantation, coinciding with suture removal, followed by regular follow-up visits every 6 months, depending on the patient's underlying conditions. One of the major advantages of telemonitoring systems is that, under optimal circumstances, they allow for a prolongation or even doubling of the interval between in-person follow-up visits.

The principle of telemonitoring is based on the transmission of diagnostic data stored in the device memory to the manufacturer's central server, either through patient-initiated transmissions or automatically at predefined intervals. In addition, the occurrence of certain predefined adverse events may trigger automatic alert notifications. The treating physician can review the transmitted data via the manufacturer's platform; however, the stored information cannot be modified and the device cannot be remotely reprogrammed. (Figure 6).

1. Patient implanted with a CIED equipped for telemonitoring,
2. remote monitoring transmitter (automated or patient-triggered transmissions),
3. monitoring center with secured domain,
4. monitoring service center with dedicated nurses with "triage training",

5. treating physician receiving an alert-triggered referral from 4.

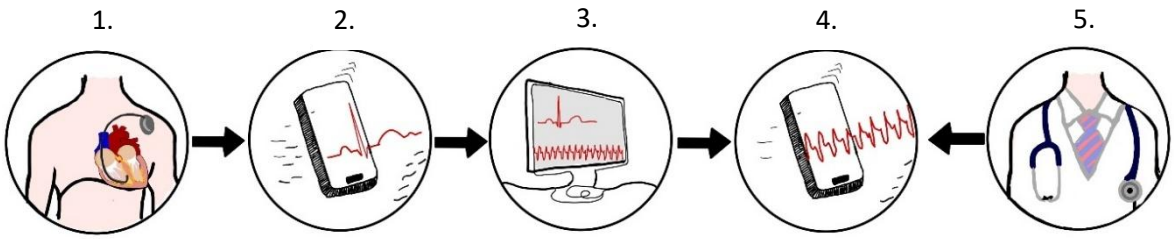


Figure 6. Telemonitoring Systems and Data Transmission Units (own illustration)

The COVID-19 pandemic served as a unique feasibility and endurance test for telecardiology systems, as it imposed unprecedented constraints on conventional, in-person outpatient care. During this period, remote monitoring was evaluated across a broad range of CIED populations, regarding both patients with heart failure and those treated with ICD, studied in combined cohorts as well (83, 84, 85, 86).

According to current ESC guidelines, remote monitoring should be applied as a complementary tool alongside standard care, particularly in high-risk patients with heart failure (1). Nevertheless, uncertainties remain regarding its optimal integration into long-term management and the identification of patient subgroups deriving the greatest clinical benefit.

2. Aims

The aim of this dissertation is to investigate clinically interconnected aspects of SCA and advanced cardiovascular care. The first two studies focus on population-level risk factors and early post-resuscitation intensive care management in patients with OHCA, while the third study addresses long-term cardiovascular follow-up and remote monitoring in a broader high-risk cardiac population treated with cardiac implantable electronic devices.

2.1. Temperature-Related Patterns of Out-of-Hospital Cardiac Arrest

The objective of this study was to assess the impact of extreme temperature changes, particularly extreme cold and heat exposure, on the population-level incidence of OHCA. Additional aims included the evaluation of non-linear and delayed effects, as well as the exploration of whether the temporal pattern of temperature-related risk differs across distinct exposure ranges.

2.2. Early Prognostic Assessment after Return of Spontaneous Circulation: Development and Validation of the RAPID Score during Targeted Temperature Management

The aim of the study was to identify clinical and laboratory factors available within the first 12 hours after intensive care admission that are associated with 30-day mortality in patients with OHCA treated with targeted temperature management, and to evaluate these variables within a predictive modelling framework, complemented by the development of an internally validated and clinically applicable prognostic scoring system.

2.3. Long-term Cardiovascular Follow-Up and Device-Based Remote Monitoring in High-Risk Cardiac Patients

Lastly, the objective of this study was to evaluate long-term outcomes in high-risk patients with heart failure and cardiac implantable electronic devices, with particular emphasis on the progression of heart failure and arrhythmogenesis, the role of device-based therapy, and the clinical value of remote monitoring. A further aim was to assess how telemonitoring may contribute to maintaining clinical stability and continuity of care in altered healthcare environments.

3. Methods

All studies forming the basis of this dissertation were conducted in accordance with the principles of the Declaration of Helsinki and applicable Hungarian legislation.

3.1. Study Design and Statistics for Temperature-Related Patterns of Out-of-Hospital Cardiac Arrest

We conducted a nationwide, population-based time-series analysis by linking the comprehensive out-of-hospital cardiac arrest surveillance database of the Hungarian National Ambulance Service with meteorological data provided by Hungarian Meteorological Service (HungaroMet). The study period covered 1,887 consecutive days between 1 November 2018 and 31 December 2023, encompassing multiple seasonal cycles and several extreme weather events. All adults aged 18 years or older were included if cardiopulmonary resuscitation was initiated by emergency medical services for a presumed origin of OHCA. The study was performed using anonymized, secondary national ambulance service and meteorological databases. The study was approved by the competent research ethics authority (Reference Numbers: IV/3043/2021/EKU and IV/3043-3/2021/EKU), and individual patient information and written informed consent were not required due to the retrospective, non-interventional method.

From the initial database, traumatic events, suicide attempts, intoxication-related cases, drowning- and obstetric-related cardiac arrests were excluded, as well as cases in which geographical localization or linkage to meteorological data could not be reliably established. We also excluded events in which emergency medical services performed death certification without resuscitation attempts, as these cases are more likely to reflect delayed recognition of death, particularly during colder periods. The final analytical population comprised 116,579 non-traumatic OHCA cases attended by emergency medical services.

Meteorological exposures were defined using season- and percentile-based thresholds tailored to local climatic conditions, taking into account population-level adaptation to temperature stress. Primary exposures included heatwaves, cold spells, and severe cold days. Heatwave and cold-spell definitions were based on percentiles of the Hungarian temperature distribution: the 95th percentile during the warm season and the 2nd percentile during the cold season were used as threshold values. These cut-offs were

aligned with the thresholds applied in the heat-health early warning system of the Hungarian National Public Health Center.

- Primary heatwave: ≥3 consecutive days with a daily mean temperature ≥27.1 °C, corresponding to the 95th percentile of warm-season (May-September) temperatures.
- Primary cold spell: ≥2 consecutive days with a daily minimum temperature ≤-9.2 °C, corresponding to the 2nd percentile of cold-season (November-March) temperatures.
- Severe cold day: any single day with a minimum temperature below -10 °C.

To evaluate the robustness of the primary analyses and to capture a broader range of meteorological conditions, several secondary exposures were also examined.

The following secondary exposures were defined.

- Hot day: daily maximum temperature ≥35 °C.
- Tropical night: daily minimum temperature ≥20 °C.
- Alternative heatwaves:
    - ≥2 consecutive days with mean temperature ≥27.1 °C (95th percentile),
    - ≥2 consecutive days with mean temperature ≥28.2 °C (98th percentile),
    - ≥2 consecutive days with mean temperature ≥28.8 °C (99th percentile).
- Alternative cold spells:
    - ≥2 consecutive days with minimum temperature ≤-6.0 °C (5th percentile),
    - ≥2 consecutive days with minimum temperature ≤-12.1 °C (1st percentile),
    - ≥3 consecutive days with minimum temperature ≤-6.0 °C (5th percentile).
- Low solar radiation: ≤109.0 J/cm² (25th percentile).
- High solar radiation: ≥281.4 J/cm² (75th percentile).

- Low relative humidity: <50%.
- High relative humidity: >70%.

Completeness of daily meteorological data exceeded 99.5% over the study period.

Daily OHCA counts exhibited substantial overdispersion; therefore, negative binomial regression models were used for the primary analyses. To reduce potential temporal confounding, models included fixed effects for day of the week, calendar month, and year, thereby accounting for weekly patterns, seasonal variability, and long-term trends. Residual temporal correlation was addressed using cluster-robust standard errors at the year-month level.

To isolate the independent effect of extreme temperature events, an "added-effect" modeling approach was applied, in which binary indicators for heatwaves and cold spells were included alongside natural cubic spline functions describing the non-linear association between daily temperature and OHCA risk. Distributed lag non-linear models were used to assess delayed effects of temperature exposure, applying a 21-day lag window and a reference temperature corresponding to the minimum mortality temperature. This approach allowed characterization of distinct temporal risk patterns associated with heat and cold exposures. A 21-day lag window was selected based on previous environmental epidemiological studies and on the established delayed and cumulative nature of cold-related cardiovascular effects, which may persist substantially longer than heat-related effects.

Sex-stratified subgroup analyses were performed by fitting separate regression models, and formal interaction tests were conducted to evaluate effect modification between sex and extreme temperature exposures. Robustness of the findings was assessed through multiple sensitivity analyses, including alternative model specifications, seasonal exclusions, and different clustering strategies.

Data preprocessing and primary regression analyses were conducted in a Python environment, while analyses of delayed effects were performed using R statistical software. Statistical significance was defined as a two-sided p-value < 0.05.

3.2. Study Design and Statistics for Early Prognostic Assessment after Return of Spontaneous Circulation: Development and Validation of the RAPID Score during Targeted Temperature Management

We conducted a single-center, retrospective, non-interventional study at the Városmajor Heart and Vascular Center of Semmelweis University between 1 January 2016 and 31 December 2022. Adult patients (≥18 years) were included if they suffered an out-of-hospital cardiac arrest, remained comatose after return of spontaneous circulation, and were admitted to the cardiac intensive care unit, where early targeted temperature management was initiated. According to the institutional protocol, temperature control was applied in patients fulfilling predefined institutional eligibility criteria, including successful cardiopulmonary resuscitation was achieved within 30 minutes, and admission core temperature exceeded 30 °C. During the study period, a uniform target temperature of 33 °C was applied in all eligible patients.

Exclusion criteria included age under 18 years, pregnancy, terminal underlying disease, known coagulopathy or cryoglobulinemia, and cases in which next of kin refused consent for retrospective data processing. Patients were also excluded if coma was attributable to causes other than cardiac arrest, such as intoxication, electrolyte disturbances of any origin, trauma, cerebrovascular events, or status epilepticus. In hemodynamically unstable patients, exclusion criteria included persistent mean arterial pressure below 60 mmHg lasting more than 30 minutes despite the use of more than two vasopressors, uncontrollable malignant arrhythmias, active bleeding, or prolonged severe hypoxemia (87). Additional exclusion criteria were discontinuation of targeted temperature management within the first 24 hours and missing clinical data related to the circumstances of cardiac arrest or initial medical care. The study was approved by the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University (SE RKEB approval number: 194/2020). Data were processed in anonymized form within the framework of the patients' general consent related to routine clinical care.

During the study period, data from 135 consecutive patients selected for targeted temperature management were assessed. Missingness was predominantly related to prehospital parameters due to incomplete EMS documentation during the early study period. Therefore, patients with more than 10% missing data across the evaluated parameters were excluded from the final modelling cohort. Accordingly, 27 patients were

excluded due to missing data, two due to age criteria, and three due to cardiogenic shock-related death within the first 12 hours of cooling. The final analytical cohort included only patients who fulfilled all inclusion criteria. Detailed inclusion and exclusion criteria are presented in Table 2. Written informed consent for data processing was obtained from the patients or their legal representatives.

Data collection was performed using hospital electronic medical records, intensive care nursing charts, and reports from the Hungarian National Ambulance Service. Recorded variables included demographic characteristics, etiology of cardiac arrest, durations of prehospital and intrahospital care, admission laboratory and arterial blood gas parameters, echocardiographic characteristics, and respiratory and/or circulatory support therapies required within the first 24 hours.

Table 2. Study design and eligibility criteria of the study population

Abbreviations: ROSC: return of spontaneous circulation; CPR: cardiopulmonary resuscitation; TTM: targeted temperature management; INR: international normalized ratio; aPTT: activated partial thromboplastin time; MAP: mean arterial pressure; O_2: oxygen.

Category	**Detailed Criteria**
Inclusion criteria	Age ≥ 18 years
	Out-of-hospital cardiac arrest
	Comatose after ROSC or sedated and mechanically ventilated due to prolonged arrest-to-ROSC interval
	Maximum 5–15 min from cardiac arrest to initiation of full medical care
	Successful CPR within 30 min
	Initial body temperature > 30 °C
Exclusion criteria	Pregnancy
	Age < 18 years
	Terminal illness
	Known coagulopathy or cryoglobulinemia
	Refusal of consent for retrospective data analysis

	Coma unrelated to cardiac arrest (intoxication, electrolyte imbalance, trauma, cerebrovascular accident, status epilepticus)
	Active bleeding (INR > 3.0; aPTT > 3× normal; platelet count < 50,000/mm³)
	Mean arterial pressure < 60 mmHg for > 30 min requiring > 2 vasopressors (e.g., norepinephrine and adrenaline or vasopressin/terlipressin)
	Prolonged hypoxemia (O_2 saturation < 85% for > 20 min)
	Unstable arrhythmia not correctable
	Interruption of TTM within the first 24 h
	Missing clinical data concerning arrest circumstances or first response
	>10% overall data loss

The primary outcome was 30-day mortality. Date of death was determined using the database of the National Health Insurance Fund Administration, supplemented by data from the national electronic health record system. Targeted temperature management was performed using surface cooling devices in all patients, consisting of an induction phase followed by a maintenance phase at a target temperature of 33 °C (range 32-34 °C) and a controlled rewarming phase with a rate not exceeding 0.25-0.5 °C per hour.

In statistical analyses, categorical variables were expressed as absolute numbers and percentages, while continuous variables were presented as medians with interquartile ranges. Group comparisons were performed using Fisher's exact test and the Mann-Whitney U test, as appropriate. The proportion of missing data was low and was handled using single imputation. Prognostic model development was performed using nonlinear logistic regression, with relationships between continuous predictors and outcome assessed using restricted cubic splines. Variable selection was carried out using a combination of stepwise backward elimination and bootstrap resampling, guided by the Akaike information criterion (AIC). Model discrimination in the development cohort was first evaluated using the apparent area under the receiver operating characteristic curve (AUC), while calibration was assessed using calibration slope and intercept. Internal validation was subsequently performed with 10,000 bootstrap resamples to obtain optimism-adjusted performance estimates.

3.3. Study Design and Statistics for Long-term Cardiovascular Follow-Up and Device-Based Remote Monitoring in High-Risk Cardiac Patients

We conducted a single-center, retrospective study at the Heart and Vascular Center of Semmelweis University between 1 January 2020 and 31 August 2020. Adult patients (≥18 years) with a CIED equipped with a remote monitoring function were eligible for inclusion. The analysis was limited to patients who fulfilled all inclusion criteria. Cases with incomplete clinical documentation and patients whose CIED follow-up was performed at another institution were excluded. The study was approved by the relevant institutional research ethics committee (approval number: 106/2020). Patient data were analyzed in anonymized form, in compliance with applicable data protection regulations.

Three distinct study periods were defined according to changes in healthcare organization related to the COVID-19 pandemic: the pre-pandemic period (1 January 2020 to 15 March 2020), the lockdown period affected by pandemic-related restrictions (15 March 2020 to 18 June 2020), and the post-lockdown period following the lifting of restrictions (19 June 2020 to 31 August 2020).

Throughout the study period, the management of patients with CIEDs followed the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy, and the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, in addition to institutional protocols. After device implantation, patients routinely attended an outpatient follow-up visit one week later, during which wound inspection and verification of device function were performed, as lead dislodgement and sensing and pacing issues most frequently occur in the early postoperative period. Subsequent follow-up visits were scheduled every 6-12 months, depending on device type, device age, the patient's clinical condition, and underlying cardiac disease. During in-person visits, a comprehensive cardiology examination and full device interrogation and, if necessary, reprogramming was performed by an electrophysiology specialist. Unscheduled visits were arranged if device malfunction or clinical deterioration was suspected.

Following the introduction of pandemic-related restrictions, non-urgent medical care was postponed, and a substantial proportion of patients were unable to attend scheduled in-

person follow-up visits. During this period, patient assessment was performed via telephone consultations, complemented by the evaluation of remote monitoring data. The number of outpatient visits was determined using the central hospital information system, which automatically recorded all institutional encounters. To assess changes in outpatient care volume, two periods were compared, as this analysis focused on year-over-year differences in overall visit frequency: the one-year pre-pandemic period (16 March 2019 to 15 March 2020) and the first year of the pandemic (16 March 2020 to 15 March 2021). In contrast, analyses of device-derived parameters and patient status assessments were performed across three predefined study periods, reflecting distinct phases of healthcare organization during the pandemic.

As an objective indicator of disease progression, the occurrence of acute heart failure decompensations was also analyzed. These events were defined as emergency cases requiring immediate hospital admission and were identified through the National eHealth Infrastructure, regardless of whether treatment occurred at our institution or elsewhere.

Remote monitoring data included device-recorded parameters related to heart failure status and arrhythmias, such as the proportion of intrinsic and paced rhythm, percentage of CRT pacing, patient activity, heart rate variability, malignant arrhythmia episodes, and the number of ventricular premature beats per hour. For analytical purposes, all device-derived parameters were stratified according to the three predefined study periods corresponding to different phases of healthcare organization during the COVID-19 pandemic: the pre-pandemic period (1 January 2020-15 March 2020), the lockdown period (15 March 2020-18 June 2020), and the post-lockdown period (19 June 2020-31 August 2020).

Patient-reported symptoms and quality of life were assessed using validated questionnaires. The Kansas City Cardiomyopathy Questionnaire was used to evaluate heart failure-related symptoms and functional status, while the EQ-5D-5L questionnaire assessed general health status (88, 89). Questionnaires were administered during telephone consultations, and patients were asked to provide responses retrospectively for each of the three above mentioned study periods.

In addition to remote monitoring data, demographic and clinical information was collected from outpatient records and hospital databases, including age, sex, and major

comorbidities such as hypertension, diabetes mellitus, dyslipidemia, thyroid disease, chronic kidney disease, heart failure, coronary artery disease, acute and chronic coronary syndrome, arrhythmia types, and chronic lung disease.

Statistical analyses included descriptive statistics, Pearson's chi-square test, Kruskal-Wallis and ANOVA tests, and the Wilcoxon-Friedman test. Continuous variables were expressed as mean ± standard deviation, and categorical variables as absolute numbers and percentages. Statistical significance was defined as a two-sided p value < 0.05. Data processing was performed using Microsoft Excel, and statistical analyses were conducted with IBM SPSS software.

4. Results

4.1. Temperature-Related Patterns of Out-of-Hospital Cardiac Arrest

During the 1,887-day study period, 116,579 adult OHCA cases were analyzed. The median daily incidence was 60 cases (IQR 52-69). The mean age of patients was 69 years, and 59% were male. Most events occurred at home (80.5%). Daily mean temperature ranged between −6.8 °C and 30.6 °C. Extreme temperature events were infrequent, with 20 heatwave days, 14 cold spell days, and 12 severe cold days. Baseline epidemiological and meteorological characteristics are summarized in Table 3.

Table 3. Baseline epidemiological and meteorological characteristics of the Hungarian OHCA cohort and study period. Values are shown for the complete 5.2-year dataset.

Abbreviations: IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; SD, standard deviation.

Characteristic	Value
Study Period and Analytical Scope	
Total analysis days, n	1,887
Study duration	5.2 years
Date range	1 November 2018 - 31 December 2023
Out-of-Hospital Cardiac Arrest Cases	
Total OHCA cases, n	116,579
Daily OHCA count, median (IQR)	60.0 (52.0-69.0)
Daily OHCA count, range	28-102
Patient Demographics	
Mean age ± SD, years	69.4 ± 14.3
Male patients, n (%)	68,735 (59.0)
Female patients, n (%)	47,844 (41.0)
Location of OHCA	
Home, n (%)	93,808 (80.5)
Public areas, n (%)	12,271 (10.5)
Other locations, n (%)	10,500 (9.0)
Meteorological Exposure Summary	
Daily mean temperature range, °C	-6.8 - 30.6
Primary heatwave days, n (%)	20 (1.1)
Primary cold spell days, n (%)	14 (0.7)
Individual severe cold days, n (%)	12 (0.6)
Temperature Thresholds	
Heatwave threshold (95th percentile), °C	27.1

Characteristic	Value
Cold spell threshold (2nd percentile), °C	-9.2
Severe cold threshold, °C	-10.0

Distributed lag non-linear modeling demonstrated a non-linear association between daily mean temperature and OHCA incidence over the 21-day lag period (Figure 7). The lowest cumulative risk was observed at a mean temperature of 19.0 °C. Deviations from this temperature were associated with increasing OHCA risk, with a more pronounced rise at lower temperatures compared to higher temperatures.

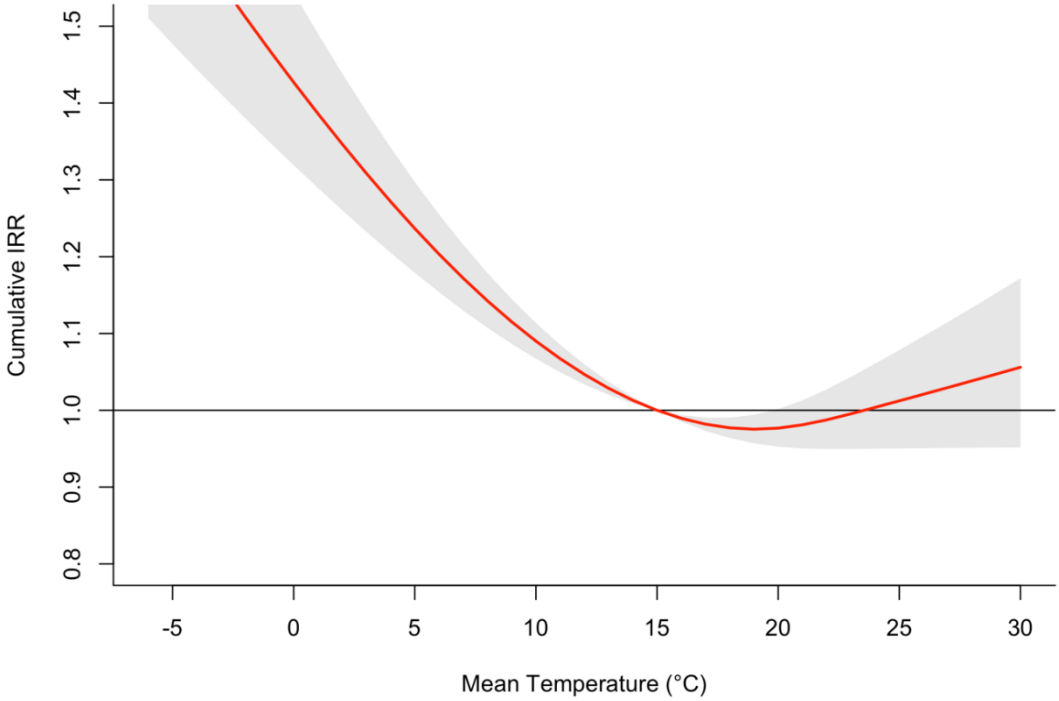


Figure 7. Overall Cumulative Exposure-Response (source: Nagy B, et al. Resuscitation Plus. 2026;27:101194. CC BY 4.0).

Cumulative association between daily mean temperature and OHCA risk over a 21-day lag, estimated with distributed lag non-linear models. The curve shows a U-shaped relationship with lowest risk at 19.0°C (minimum mortality temperature). Risk increases towards both heat and cold extremes, with steeper effects for cold. The red line indicates the estimated cumulative IRR; grey shading indicates 95% confidence intervals. Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MMT, minimum mortality temperature; OHCA, out-of-hospital cardiac arrest.

Lag-response analysis revealed distinct temporal patterns for heat and cold exposures (Figure 8). High temperatures were associated with an immediate increase in OHCA risk, with the effect peaking during the first few days after exposure and diminishing within one week. In contrast, low temperatures showed a delayed onset, with risk increasing after several days and persisting across the full 21-day lag period.

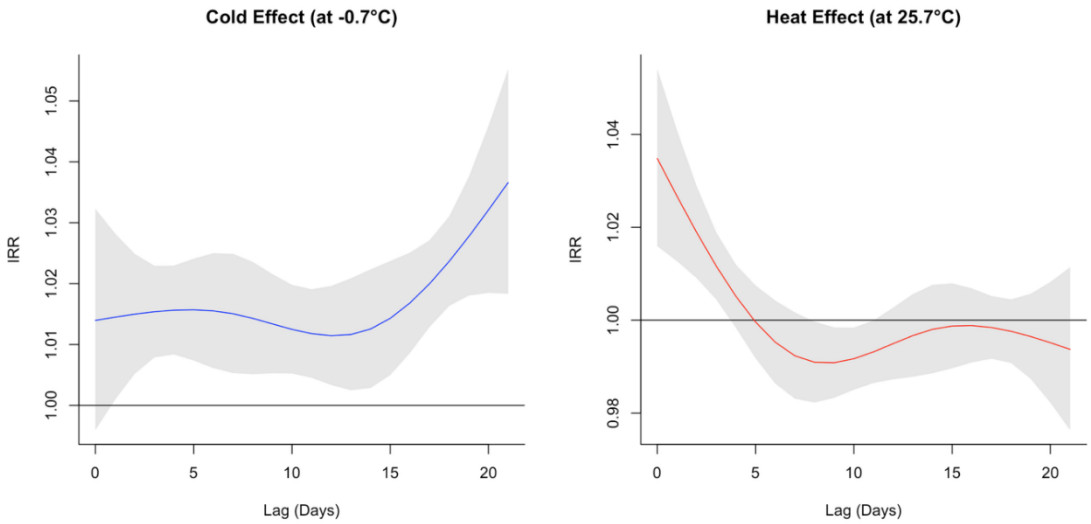


Figure 8. Lag-Specific Effects of Cold and Heat Exposure on OHCA Incidence (source: Nagy B, et al. Resuscitation Plus. 2026;27:101194. CC BY 4.0).

Lag-response associations between ambient temperature and OHCA incidence over a 21-day period estimated using distributed lag non-linear models. Effects are shown relative to the minimum mortality temperature (19.0 °C). Heat exposure (95th percentile, 25.7 °C) was associated with an early, transient increase in risk, whereas cold exposure (5th percentile, −0.7 °C) demonstrated a delayed and more sustained effect. Solid lines indicate point estimates and shaded areas represent 95% confidence intervals. The temperature percentiles illustrated reflect the exposure distribution used in the DLNM framework and differ from the thresholds applied for sustained extreme events in the primary analyses. Abbreviations: CI, confidence interval; DLNM, distributed lag non-linear model; IRR, incidence rate ratio; OHCA, out-of-hospital cardiac arrest.

Using added-effect models, all predefined extreme temperature exposures were independently associated with increased daily OHCA incidence (Table 4). The strongest association was observed for cold spells, which were linked to an approximately 19% higher incidence of OHCA. Severe cold days were also associated with a significant risk increase, while sustained heatwaves showed a more modest but still statistically significant effect.

Table 4. Independent effects of extreme temperature exposures on daily OHCA incidence.

Independent incidence rate ratios were estimated using added-effect models adjusting for the underlying non-linear temperature-risk relationship.
Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OHCA, out-of-hospital cardiac arrest.

Exposure Category	**Definition**	**IRR (95% CI)**	**p-value**
Extreme Heat	Sustained heatwave: ≥3 consecutive days with T_{avg} ≥ 27.1°C (95th percentile)	1.110 (1.032-1.195)	0.005
Extreme Cold	Cold spell: ≥2 consecutive days with T_{min} ≤ -9.2°C (2nd percentile)	1.189 (1.089-1.299)	<0.001

Exposure Category	Definition	IRR (95% CI)	p-value
Extreme Cold	Severe cold day: Single day with T_{min}< -10°C	1.143 (1.012-1.291)	0.031

Sensitivity analyses confirmed the robustness of these associations. As illustrated in Figure 9, varying the heatwave definition across higher percentile thresholds yielded consistent effect estimates. Comparable stability was observed for alternative cold-exposure definitions in the original article supplementary analyses (90).

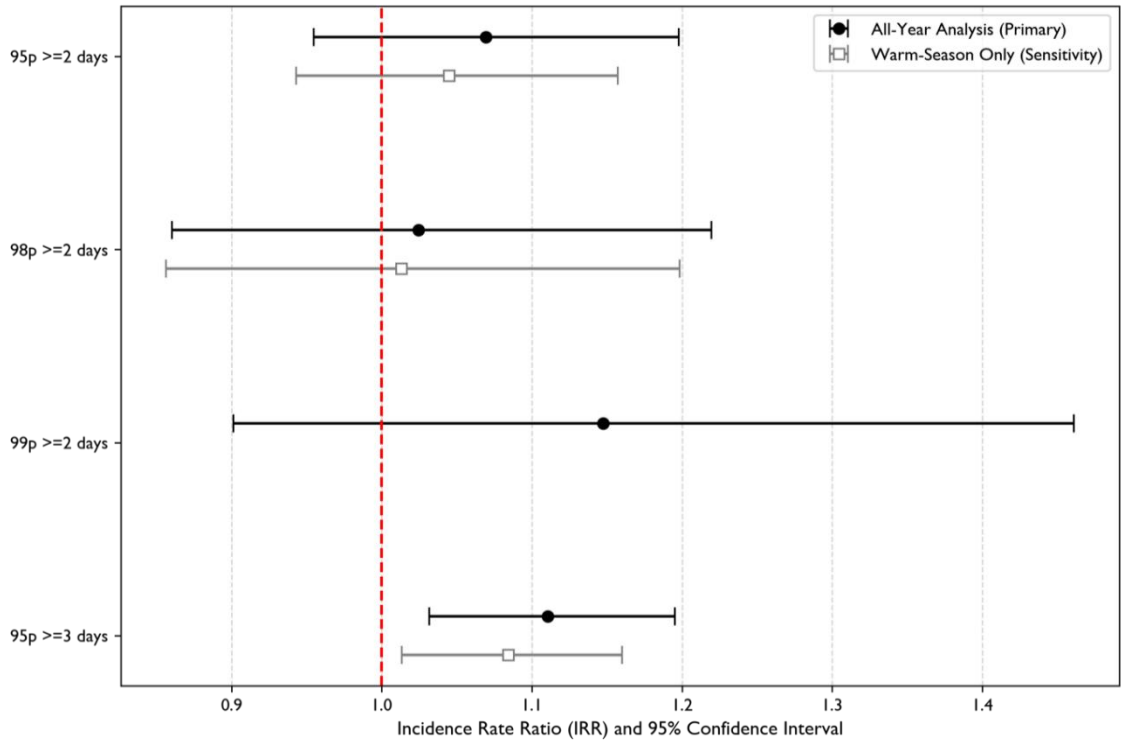


Figure 9. Added effect of heatwaves on OHCA incidence (source: Nagy B, et al. Resuscitation Plus. 2026;27:101194. CC BY 4.0).

Estimated excess OHCA risk attributable to sustained heat events after accounting for the background temperature-risk curve. Points represent incidence rate ratios and error bars indicate 95% confidence intervals. The vertical reference line denotes no added effect (IRR = 1.0). The y-axis shows the alternative sustained heatwave definitions used in the sensitivity analyses, where 95p, 98p, and 99p refer to the 95th, 98th, and 99th percentiles of the daily mean temperature distribution, respectively; heatwaves were defined as periods of at least two consecutive days exceeding these percentile-based thresholds. Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OHCA, out-of-hospital cardiac arrest.

Secondary meteorological variables, including relative humidity, solar radiation, isolated hot days, and tropical nights were not significantly associated with daily OHCA incidence. A detailed evaluation of these secondary exposures is presented in the published article and its supplementary material (90). Overall, these findings indicate that

the observed excess risk was specific to sustained extreme temperature exposures rather than to other weather-related factors.

4.2. Sex differences and effect modification

Formal interaction analyses did not demonstrate statistically significant sex-based effect modification in the association between extreme temperature exposures and OHCA incidence (global interaction $p = 0.226$). In sex-stratified models, sustained heatwaves were associated with a comparable increase in OHCA risk among men (IRR 1.114, 95% CI 1.024-1.212) and women (IRR 1.203, 95% CI 1.097-1.319). For cold spells, point estimates were slightly higher in women than in men; however, confidence intervals overlapped, and estimates in women were less stable due to the limited number of cold spell exposure days and female cases. Detailed sex-specific estimates and robustness assessments are provided in the original publication and its supplementary materials. In the absence of statistically significant interaction, all primary analyses were therefore conducted in the pooled population.

4.3. Sensitivity and Robustness Analyses

The robustness of the main findings was confirmed through multiple sensitivity analyses. Across all model specifications, negative binomial regression consistently provided a superior fit compared with Poisson regression, with an Akaike Information Criterion difference exceeding 320 units. In leave-one-season-out validation analyses, the association between cold spells and OHCA incidence remained statistically significant in five out of six seasonal exclusions, while the heatwave effect persisted in three out of five scenarios. Detailed sensitivity analyses and alternative model specifications are presented in the published supplementary material.

4.4. Validation Against Operational Alert Criteria

Comparison with official alert thresholds issued by the Hungarian Meteorological Service provided external validation for the observed associations. Days meeting national heatwave alert criteria were associated with a significantly increased incidence of OHCA, in line with both the primary and alternative sustained heatwave definitions applied in this analysis. Likewise, days classified as severe cold alerts by the Hungarian Meteorological Service corresponded closely to the study's severe cold day definition and

were also associated with elevated OHCA risk. Detailed comparisons with operational alert thresholds are presented in the original publication and its supplementary materials.

4.5. Early Prognostic Assessment after Return of Spontaneous Circulation: Development and Validation of the RAPID Score during Targeted Temperature Management

The study included 103 adult patients admitted after OHCA, with baseline characteristics summarized in Table 5. The median age of the cohort was 58 years, and 32.1% of patients were female. We created two groups based on 30-day mortality: survivors and non-survivors. No statistically significant differences were observed between the two groups with respect to sex distribution, cardiovascular risk factors, comorbidities, or arrest etiology. Age differed significantly between the two groups, with non-survivors being older than survivors (62.0 vs. 54.8; p = 0.007). A shockable initial rhythm was more frequently observed among survivors than among non-survivors (91.4% vs. 68.9%; p = 0.030.

Table 5. Basic characteristics of patients

The "survivor" group (S) comprises participants who survived the observed period, such as the 30-day monitoring period. The "non-survivor" group (NS) consists of participants who did not survive this period.

Abbreviations: BMI: body mass index, CABG: coronary artery bypass graft, CV: cardiovascular, IQR: interquartile range, n: number, NSTEMI: non-ST-elevation myocardial infarction, PAD: peripheral arterial disease, STEMI: ST-elevation myocardial infarction, TIA: transient ischemic attack, VF: ventricular fibrillation, VT: ventricular tachycardia

	Total	**Non-survivors**	**Survivors**	**p-value**
Baseline characteristics				
Patients (n)	103	45	58	-
Female, n (%)	33 (32.1)	12 (26.7)	21 (36.2)	0.395
Age, year (IQR)	57.9 (50.5-65)	62 (55.0-69.0)	54.8 (45.3-63.8)	0.007
BMI kg/m^2 (IQR)	28.8 (25.9-31.1)	28.9 (26.1-31.1)	28.7 (25.4-31.2)	0.727
Known CV disease, n (%)	38 (36.9)	16 (35.6)	22 (37.9)	0.839
Hypertension, n (%)	49 (47.6)	23 (51.1)	26 (44.8)	0.554
Diabetes mellitus, n (%)	23 (22.3)	13 (28.9)	10 (17.2)	0.233
Hyperlipidemia, n (%)	14 (13.6)	9 (20.0)	5 (8.6)	0.146
Prior myocardial infarction, n (%)	14 (13.6)	7 (15.6)	7 (12.1)	0.773
PAD, n (%)	8 (2.0)	6 (13.3)	2 (3.4)	0.077
Prior CABG, n (%)	4 (7.8)	2 (4.4)	2 (3.4)	1.000
Prior stroke, n (%)	3 (2.9)	2 (4.4)	1 (1.7)	0.579
Etiology				

	Total	Non-survivors	Survivors	p-value
Cardiac origin of cardiac arrest, n (%)	98 (95.1)	41 (91.1)	57 (98.2)	0.165
STEMI, n (%)	72 (69.9)	29 (64.4)	43 (74.1)	0.387
NSTEMI, n (%)	3 (2.9)	1 (2.2)	2 (3.4)	1.000
Acute decompensation of heart failure, n (%)	9 (8.7)	3 (6.6)	6 (10.3)	0.728
Cardiomyopathy, n (%)	9 (8.7)	6 (13.3)	3 (5.2)	0.174
Valvular disease, n (%)	3 (2.9)	0	3 (5.4)	0.255
Other, n (%)	2 (1.9)	2 (4.4)	0	0.188
Non-cardiac origin, n (%)	5 (4.9)	4 (8.9)	1 (1.7)	0.165
Initial rhythm				
Shockable rhythm - VT/VF (%)	84 (81.5)	31 (68.9)	53 (91.4)	0.03
Non-shockable rhythm				
Asystole (%)	10 (9.7)	6 (13.3)	4 (6.9)	0.297
Pulseless electric activity (%)	5 (4.9)	4 (8.9)	1 (1.7)	0.127
Bradycardia (%)	1 (1.0)	1 (2.2)	0	0.323
No available data	3 (2.9)	3 (6.7)	0	0.083

4.6. Predictors of 30-Day Mortality

Admission heart rate, modeled as a non-linear variable, showed the strongest relative contribution to model performance, based on changes in Akaike Information Criterion (ΔAIC = 9.2; p = 0.0013). Additional variables independently associated with higher mortality included non-shockable initial rhythm (ΔAIC = 4.8; p = 0.0093), age (ΔAIC = 4.4; p = 0.0115), low arterial pH at admission (ΔAIC = 3.7; p = 0.0171), and increased right ventricular end-diastolic diameter (RVEDD) assessed on the first echocardiographic examination after admission (ΔAIC = 2.5; p = 0.0342). The relative prognostic contribution of the selected variables is illustrated in Figure 10.

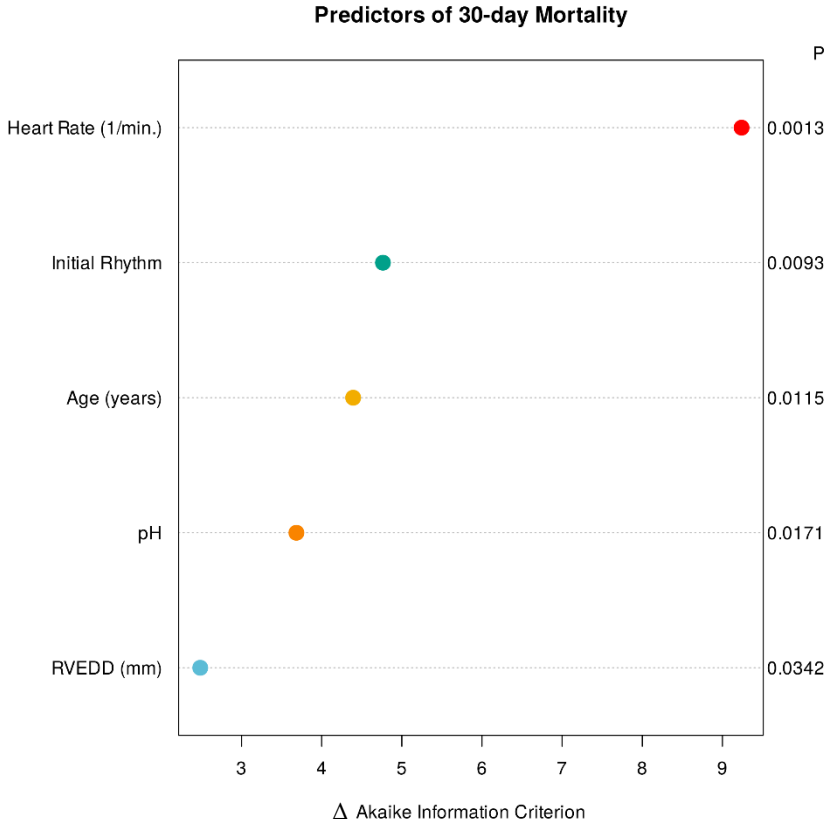


Figure 10. Relative contribution of variables to model performance in the final multivariable prognostic model(source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0).

Dot charts depict the relative contribution of each predictor to model performance based on changes in Akaike Information Criterion (ΔAIC) during the variable selection process. Higher values indicate a greater deterioration in model fit after removal of the corresponding variable from the multivariable model. P-values were derived from likelihood ratio Chi-square tests performed during model comparison. Different colors were used solely for visual distinction between variables and do not represent additional statistical information.
Abbreviations: RVEDD, right ventricular end-diastolic diameter.

The functional form of the associations between selected predictors and 30-day mortality is illustrated in Figure 11. Admission heart rate demonstrated a non-linear relationship with mortality risk, characterized by an initial decrease in predicted mortality followed by an increase at higher heart rate values. A shockable initial rhythm was associated with a lower predicted probability of 30-day mortality compared with non-shockable rhythms. Arterial pH showed an inverse association with mortality risk, with higher pH values corresponding to lower predicted mortality. In contrast, right ventricular end-diastolic diameter (RVEDD) exhibited an approximately linear positive association with the log odds of 30-day mortality.

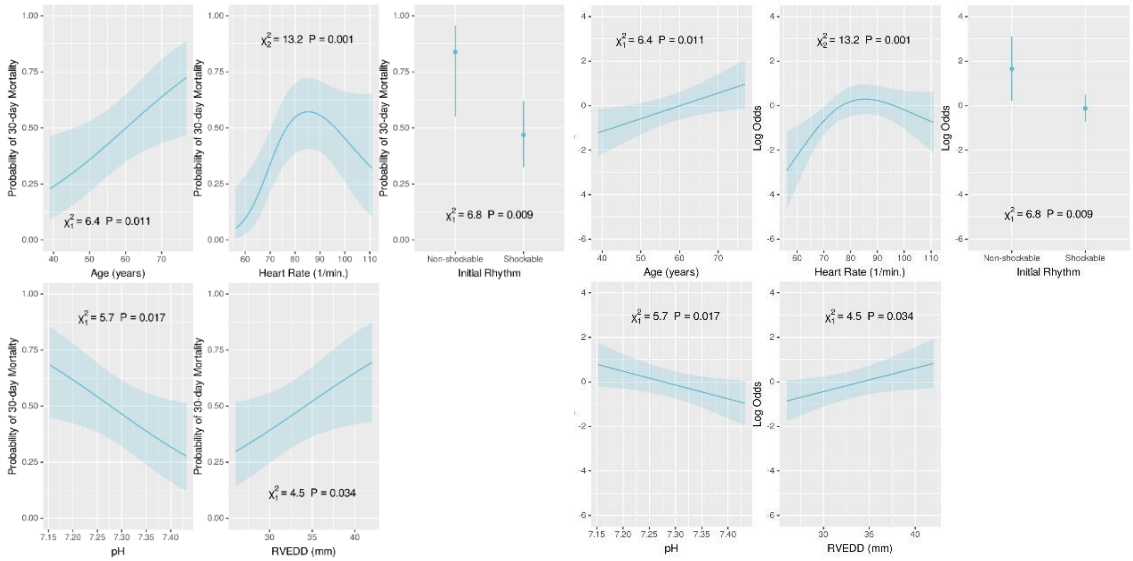


Figure 11. Relationship between various predictors and the probability and log odds of 30-day mortality in the context of TTM after OHCA (source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0).

In the plots, shaded areas represent the confidence intervals, the narrower the shaded area, the more precise the estimation is.
Abbreviations: RVEDD, right ventricular end-diastolic diameter.

The discrimination of the model was good, with an area under the receiver operating characteristic curve (AUC) of 0.8352 (bootstrapped 95% confidence interval: 0.7548-0.9069). The optimal cut-off value, determined by maximizing the Youden index, was 0.4659. At this threshold, the model achieved a sensitivity of 0.7778 and a specificity of 0.7586 (Figure 12).

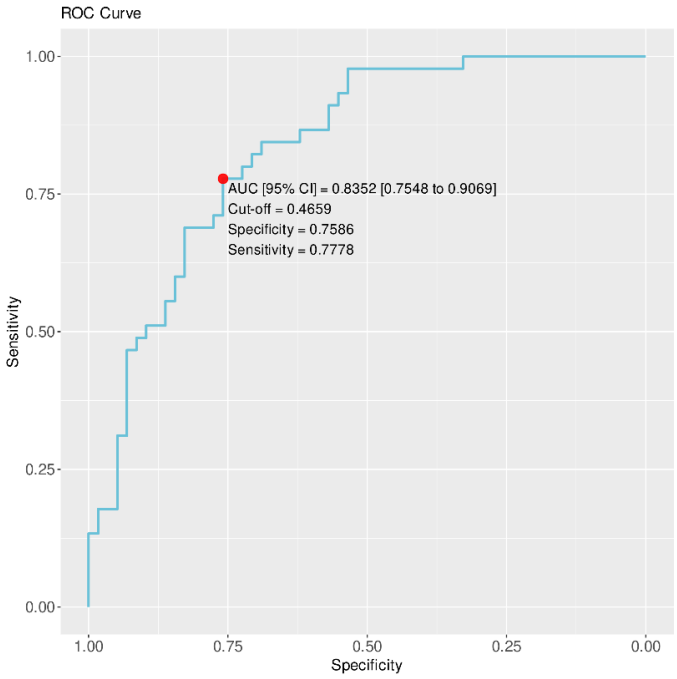


Figure 12. Receiver operating characteristic curve of the model for identifying 30-day mortality of patients treated with TTM after out-of-hospital cardiac arrest (source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0).

Abbreviations: AUC, area under curv; CI, confidence interval; TTM, targeted temperature management. Red dot represents the AUC value based on the best ratio of sensitivity and specificity.

After internal validation by bootstrap resampling with 10,000 replicates, good agreement between predicted and observed outcomes was observed, as illustrated by the calibration of the apparent and optimism-corrected models in Figure 13.

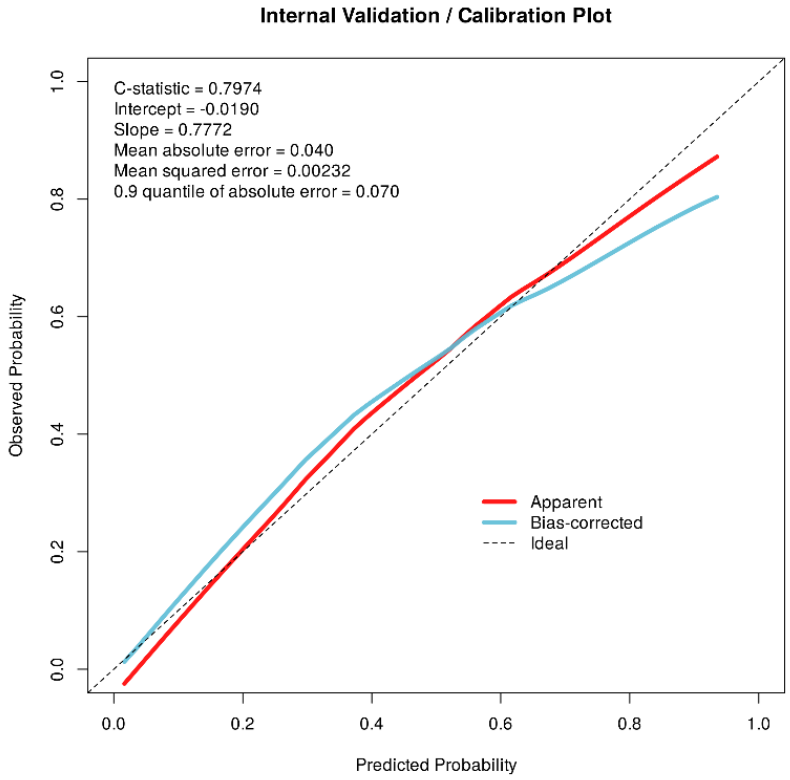


Figure 13. Calibration plot showing evaluation of the performance of the created predictive model (source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0).

4.7. Nomogram

To facilitate individualized risk estimation, a nomogram based on the final multivariable model was constructed (Figure 14). The nomogram integrates the independently associated predictors identified during model development and translates them into a visually applicable clinical risk assessment tool. By combining routinely available early intensive care parameters, the RAPID score allows individualized estimation of 30-day mortality risk in patients treated with TTM after OHCA. The score may support early prognostic assessment and clinical decision-making during the initial phase of post-

cardiac arrest intensive care. The RAPID score can be calculated using the nomogram or via the dedicated online calculator (https://www.rapidscore.eu/).

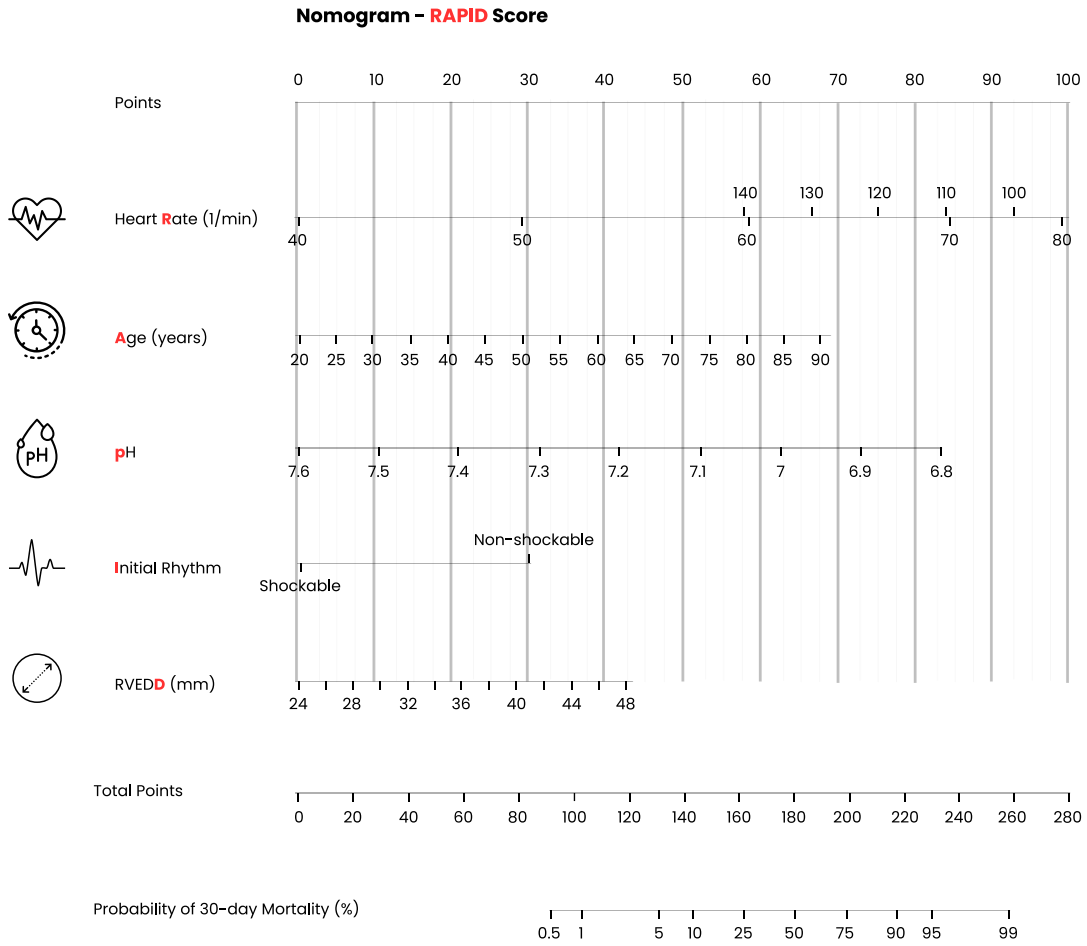


Figure 14. The RAPID score nomogram is a tool used to estimate the mortality risk for out-of-hospital cardiac arrest patients undergoing TTM (source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0).
Abbreviations: RVEDD, right ventricular end-diastolic diameter; TTM, targeted temperature management.

4.8. Long-term Cardiovascular Follow-Up and Device-Based Remote Monitoring in High-Risk Cardiac Patients

The study included 85 patients with a mean age of 68.0 years, of whom 73% were male. Device distribution comprised 41 patients (48.2%) with CRT-P, 23 patients (27.1%) with CRT-D, and 21 patients (24.7%) with conventional ICD implantation. Baseline clinical characteristics are summarized in Table 6.

Table 6. Baseline clinical characteristics

Abbreviations: COPD: chronic obstructive pulmonary disease; CRT-D: cardiac resynchronization therapy with defibrillator; CRT-P: cardiac resynchronization therapy with pacemaker; ICD: implantable cardioverter defibrillator

Parameters	Result (n=85)
Male/ female, n (%)	62 (72.9) / 23 (27.1)
Age, years (mean±SD)	68.0±9.2
CRT-P / CRT-D, n (%)	41 (48.2) / 23 (27.1)
ICD, n (%)	21 (24.7)
Hypertension, n (%)	66 (77.6)
Diabetes mellitus, n (%)	22 (25.9)
Dyslipidaemia, n (%)	39 (45.9)
Hypo- /hyperthyroidism, n (%)	8 (9.4)
Renal failure, n (%)	7 (8.2)
COPD, n (%)	5 (5.9)

4.9. Number of outpatient clinic visits and acute heart failures prior to and during the lockdown

During the lockdown period (15 March-18 June 2020), the number of in-office outpatient visits decreased by 42.5% compared with the corresponding period of the previous year. Following the lifting of restrictions (19 June-31 August 2020), a compensatory increase in outpatient visits was observed, exceeding the previous year's figures by 46.6%. When comparing the full year before and after the onset of the pandemic, 159 in-office follow-up visits were recorded prior to the lockdown, compared with 116 visits in the year following the outbreak (Figure 15).

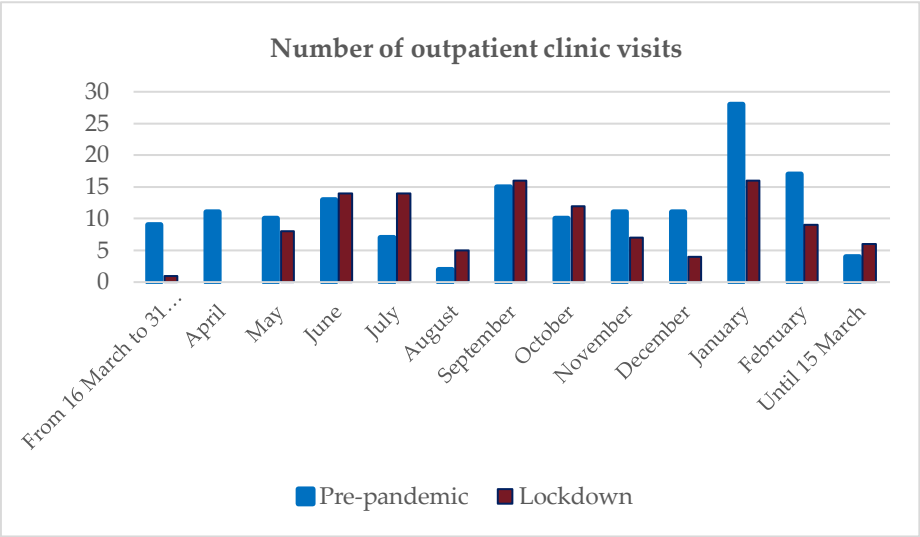


Figure 15. Number of outpatient clinic visits in the whole study population comparing identical months in the year before the lockdown and in the year following the outbreak of the pandemic (source: Nagy B, et al J Cardiovasc Dev Dis. 2023;10:214. CC BY 4.0).

The incidence of acute heart failure events did not differ significantly between the two periods. Five acute decompensation events were registered in the year preceding the lockdown, compared with seven events in the year following the outbreak (p = 0.60).

Overall, remotely monitored device parameters remained largely stable across the pre-pandemic, lockdown, and post-lockdown periods (Table 7). No statistically significant changes were observed in intrinsic rhythm, heart rate variability, atrial or ventricular pacing characteristics, ventricular arrhythmia burden, or premature ventricular activity (all p > 0.05).

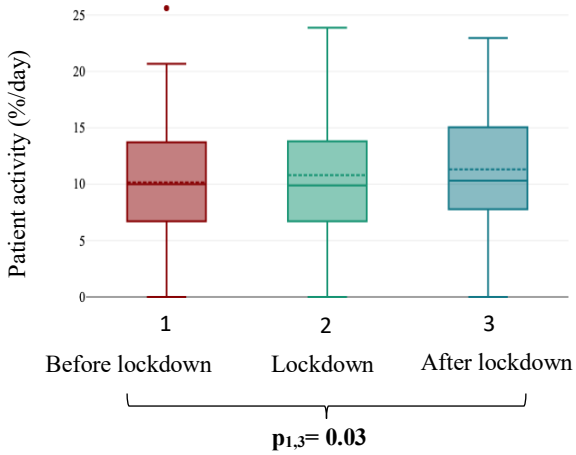
Table 7. The results of remote monitoring parameters

Abbreviations: BiV: biventricular; CI: confidence interval; CRT: cardiac resynchronization therapy; LV: left ventricle; RA: right atrium; RV: right ventricle; SD: standard deviation; VAT: ventricular pacing events that were triggered by an intrinsic atrial event; VF: ventricular fibrillation; VT: ventricular tachycardia

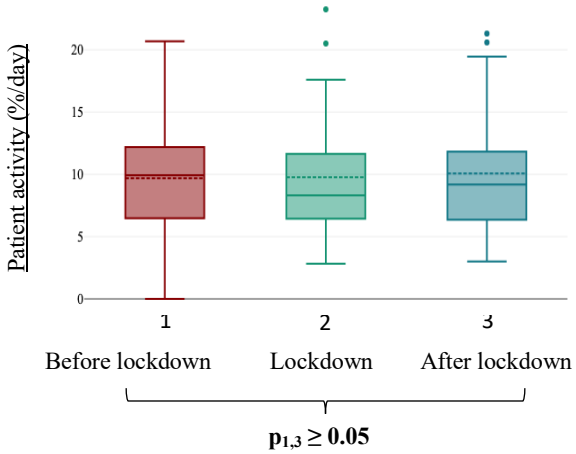
Parameter	Pre-pandemic (mean ± SD)	Lockdown (mean ± SD)	After lockdown (mean ± SD)	p-value
Atrial pacing (%)	31.2±34.4	30.4±33.2	29.6±33.2	0.931
LV pacing impedance (ohm)	734.9±257.6	741.5±254.8	755.8±287.1	0.406
BiV pacing (%)	96.0±7.2	96.1±7.5	95.1±8.9	0.225
CRT pacing (%)	98.3±2.7	98.3±2.8	97.9±3.3	0.590
LV sensing amplitudes daily mean (mV)	14.2±4.9	14.5±4.7	13.9±4.9	0.758
Mean atrial heart rate (bpm/min)	91.6±52.3	89.0±50.7	90.4±52.7	0.986
Heart rate variability (ms)	63.3±28.0	62.1±28.3	61.9±29.0	0.076
RA pacing impedance (ohm)	651.2±343.4	655.9±340.6	654.3±338.6	0.508
RV pacing impedance (ohm)	528.1±121.9	529.9±129.4	531.7±136.0	0.363
VAT stimulation (%)	61.5±36.1	62.5±34.9	61.7±34.9	0.572
VT episodes	1.8±11.4	1.8±11.4	1.9±12.1	0.941
VF episodes	0.3±0.9	0.4±1.0	0.5±1.2	0.840
Patient activity (%/day)	10.2±5.5	10.8±5.4	11.3±5.3	0.013

In contrast, patient activity showed a significant temporal change. Repeated-measures analysis demonstrated a gradual increase in daily activity levels across the three study periods ($p = 0.013$). Post-hoc testing identified a significant difference between the post-pandemic and pre-pandemic periods ($p = 0.03$). Age-stratified analyses revealed that this increase was primarily driven by patients younger than 70 years, whereas no significant change was observed in the older subgroup (Figure 16).

a) total patient population



b) subgroup by age (≥ 70 years)



c) subgroup by age (< 70 years)

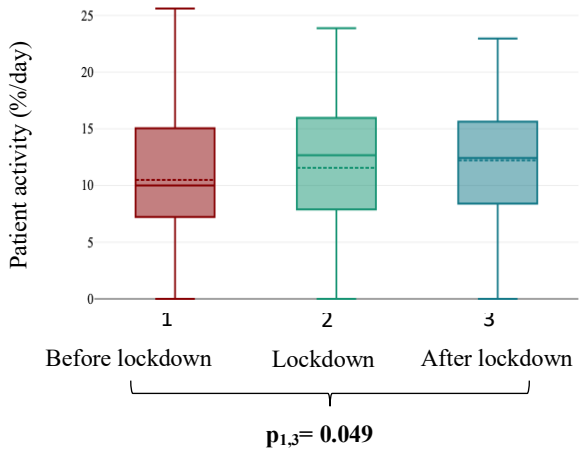


Figure 16. Analysis of patient activity (Source: Nagy B, et al J Cardiovasc Dev Dis. 2023;10:214. CC BY 4.0).

4.10. Patient-reported outcomes assessed by the Kansas City Cardiomyopathy Questionnaire and EQ-5D-5L

A total of 57 patients completed the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D-5L questionnaires (Table 8). Overall, no significant differences were observed in heart failure-related symptom burden between the pre-pandemic and lockdown periods, including fatigue, dyspnea, peripheral edema, mobility, or overall lifestyle limitation (all $p > 0.05$).

Table 8. The results of the given responses of the KCCQ and the EQ-5D-5L questionnaire (Source: Nagy B, et al J Cardiovasc Dev Dis. 2023;10:214. CC BY 4.0).

Question	Pre-pandemic (points)	Lockdown (points)	p-value
How many times has fatigue limited your ability to do what you want?	6.0±1.4	6.1±1.3	0.260
How much has your fatigue bothered you?	5.1±1.1	5.1±1.3	0.814
How much has your shortness of breath bothered you?	5.5±1.2	5.6±0.8	0.510
How many times did you have swelling in your feet, ankles or legs when you woke up in the morning?	4.6±1.0	4.7±0.7	0.455
How much does your heart failure affect your lifestyle?	4.6±0.9	4.7±0.9	0.582
How much does your heart failure affect your mobility?	1.4±1.2	1.3±1.1	0.090
How much heart failure affect visiting family or friends out your home?	4.9±0.8	5.3±1.0	<0.001
How often do you feel anxiety or depression?	1.3±0.8	1.7±1.0	<0.001

In contrast, significant changes were detected in domains reflecting psychosocial well-being. During the lockdown period, patients reported higher levels of anxiety and depression ($p < 0.001$) and a greater negative impact of heart failure on social interactions, particularly regarding visiting family and friends outside the home ($p < 0.001$).

5. Discussion

5.1. Temperature-Related Patterns of Out-of-Hospital Cardiac Arrest

Using nationwide data covering more than 116,000 out-of-hospital cardiac arrest events over a 5.2-year period, we identified a clear U-shaped, non-linear association between temperature and OHCA incidence, with the lowest risk at moderate temperatures and progressively increasing risk toward both cold and heat extremes, consistent with previous large-scale national and multicountry time-series studies of temperature-related cardiovascular outcomes (37, 91). The relatively high OHCA incidence observed in our nationwide Hungarian cohort is consistent with the most recent EuReCa-THREE registry data, which reported a confirmed OHCA incidence of 243.7 cases per 100,000 population/year and an EMS-treated OHCA incidence of 102.3 cases per 100,000 population/year in Hungary, compared with overall European incidences of 82.5 and 55.7 cases per 100,000 population/year, respectively (7). These findings further highlight that reported OHCA incidence estimates are strongly influenced by registry methodology, nationwide coverage, and the applied case definitions, including whether confirmed, EMS-assessed, or EMS-treated OHCA cases are analyzed (7).

Several landmark studies have reported similar non-linear associations between ambient temperature and cardiovascular outcomes. In a multicountry analysis including more than 74 million deaths across 384 locations worldwide, Gasparrini et al. demonstrated a U-shaped association between air temperature and mortality, with cold-related effects accounting for a substantially larger attributable burden than heat-related effects (92). Although the primary outcome of that study was all-cause mortality rather than OHCA, the overall pattern and the predominance of cold-related risk are consistent with the temperature and OHCA associations both extreme cold and heat exposures observed in the present analysis.

Our results extend these observations by focusing specifically on EMS-treated OHCA, such as a clinically well-defined and highly relevant endpoint. Prior population-based studies examining OHCA incidence have similarly reported increased risk during both cold and hot periods, with more pronounced and prolonged effects related to cold exposure (93). The use of a nationwide OHCA registry in the present analysis allows a

more direct assessment of acute, life-threatening cardiovascular events than mortality-based studies alone.

Beyond continuous temperature effects, our added-effect analyses demonstrated that sustained extreme temperature events exert an added effect on OHCA incidence. Cold spells showed the strongest association, followed by severe cold days and sustained heatwaves. Comparable event-based excess risks have been reported in studies examining prolonged heatwaves and cold spells in relation to cardiovascular mortality and emergency events, supporting the concept of cumulative physiological stress during persistent exposure (20, 21).

The predominance of cold-related effects is biologically plausible. Experimental and clinical studies indicate that cold exposure induces sustained sympathetic activation, peripheral vasoconstriction, increased blood pressure, hemoconcentration, and pro-thrombotic changes, all of which may facilitate malignant arrhythmias and sudden cardiac arrest (16, 94). In contrast, heat-related effects are typically acute and short-term, mediated by dehydration, electrolyte imbalance, and thermoregulatory stress.

The lag specific analyses further highlighted distinct temporal patterns for heat and cold effects. Heat exposure was associated with a rapid rise in OHCA risk that concentrated in the first few days after exposure, whereas cold exposure showed a later onset with a more persistent elevation of that extended across subsequent days to weeks. Comparable short-lag heat effects and longer-lasting cold-related effects have been described in cardiovascular mortality studies using distributed lag non-linear models (DLNM), which simultaneously account for non-linear exposure-response relationships and delayed effects over time. DLNM-based OHCA analyses from large registries similarly support the presence of delayed and cumulative cold-associated risk patterns (95, 96).

Notably, secondary meteorological variables, including relative humidity, solar radiation, isolated hot days, and tropical nights, did not show independent associations with OHCA incidence. As detailed in the original publication and its supplementary material, this suggests that the observed excess risk is specific to sustained extreme temperature exposure rather than to other weather-related factors. Prior large-scale epidemiological studies assessing multiple environmental parameters have similarly identified environmental temperature as the dominant meteorological driver of acute cardiovascular

risk, while the independent contributions of humidity or solar radiation appear to be limited or inconsistent (97).

We did not observe statistically significant sex-based effect modification in the association between extreme temperature and OHCA incidence. Although cold-related effect estimates were directionally higher among women, confidence intervals overlapped, and the stability of sex-stratified estimates was limited by the low number of extreme cold exposure days. While previous studies have reported sex differences in OHCA incidence, presentation, and outcomes, these analyses were not designed to evaluate effect modification by extreme temperature exposure. Consequently, existing evidence provides limited insight into whether temperature-related OHCA risk differs by sex (98, 99).

The consistency of the results across sensitivity analyses supports the methodological robustness of the findings. Negative binomial models provided a better fit than Poisson regression, reflecting overdispersion in daily OHCA counts, which is a common feature of our population-based arrest data. The persistence of both heat- and cold-related associations in leave-one-season-out analyses indicates that the observed effects were not driven by a single season or short-term anomaly, but represent a stable pattern across the study period.

In addition, the correspondence between our exposure definitions and the official alert thresholds of the Hungarian Meteorological Service shows that periods classified as heatwave or severe cold alerts coincided with higher OHCA incidence. This finding suggests that these alert categories may identify time windows during OHCA occurrence is increased, in line with the associations observed in the present analysis (7).

5.2. Early prognostic assessment after return of spontaneous circulation: development and validation of the RAPID score during targeted temperature management

In this study, we developed and internally validated the RAPID score as a simple, early prognostic tool for predicting 30-day mortality in comatose OHCA patients undergoing targeted temperature management. By focusing exclusively on parameters available within the first hours after admission, the RAPID score addresses a clinically relevant gap

in early post-cardiac arrest risk stratification, when prognostic uncertainty is highest and treatment decisions must often be made under time pressure.

The final model integrates five routinely available variables such as heart rate, age, arterial pH, initial rhythm, and right ventricular end-diastolic diameter, each reflecting a distinct pathophysiological domain of PCAS. Among these variables, admission heart rate emerged as the strongest predictor of mortality. The association was non-linear and followed an inverted J-shaped pattern, with elevated risk observed at both low and high heart rates and the lowest risk at intermediate values (Figure 10). The latter finding should be interpreted cautiously, as estimates in the high heart rate range were accompanied by wide confidence intervals, likely reflecting the limited number of patients in this subgroup.

Our findings are broadly consistent with previous studies demonstrating a favorable prognostic role of lower heart rate during TTM. A meta-analysis of 681 comatose post-cardiac arrest patients reported significantly reduced 180-day mortality in the presence of sinus bradycardia (<50 bpm) (100). Similarly, Oksanen et al. found that lower heart rate thresholds were associated with improved one-year neurological outcomes (101). These observations were further corroborated by a large multicenter cohort showing improved survival and neurological outcomes among patients with bradycardia during TTM at 33 °C (102).

Advanced age is a well-established determinant of mortality following out-of-hospital cardiac arrest (103, 104, 105). In line with previous evidence, higher age was associated with significantly increased 30-day mortality in our cohort.

Furthermore, metabolic acidosis is a key marker of global hypoperfusion and is strongly linked to adverse outcomes after cardiac arrest (106, 107, 108). In our study, arterial blood gas analysis was performed early after admission (mean 0.9 ± 1.3 h after initiation of TTM), and lower pH values independently predicted higher 30-day mortality. This inverse association likely reflects the severity and duration of tissue hypoxia and the extent of the no-flow and low-flow states associated with impaired systemic perfusion.

The prognostic value of early echocardiographic parameters after OHCA remains incompletely defined. While right ventricular dysfunction which most commonly

assessed by tricuspid annular plane systolic excursion (TAPSE) has been associated with early mortality in critically ill populations, its predictive role after cardiac arrest is inconsistent (109). In our cohort, RVEDD measured during the first 12 h of targeted temperature management independently predicted 30-day mortality ($p = 0.0342$).

RVEDD reflects right ventricular size and loading conditions, and its increase may indicate acute right ventricular dilatation related to volume overload, elevated intrathoracic pressure, or impaired ventricular compliance. During TTM, systemic vascular resistance typically rises and may be accompanied by a reduction in biventricular cardiac output. Although this response may be adaptive in maintaining arterial pressure, increased pulsatile and vascular loading conditions are not favorable for the right ventricle and may still increase right ventricular afterload, leading to myocardial strain, ventricular dilatation, and adverse outcomes. Our findings suggest that early RVEDD reflects clinically relevant right ventricular stress during temperature control and may provide incremental prognostic information beyond conventional parameters.

The RAPID score demonstrated good discriminative performance, with an AUC exceeding 0.83 and stable calibration following internal bootstrap validation. Importantly, the model relies on variables that are objective, rapidly obtainable, and largely unaffected by sedation or delayed neurological assessment due to sedation, distinguishing it from later-stage prognostic tools that incorporate neurological examination or specific biomarkers with delayed kinetics.

Several prognostic scores have been proposed for post-cardiac arrest patients, including general intensive care unit scores and arrest-specific models (67, 73, 110, 111, 112, 113). However, many of these were not designed for use in the very early phase after ROSC or require parameters that are not immediately available (67, 69, 114). In contrast, the RAPID score was explicitly developed for early application during targeted temperature management, aligning with the clinical need for timely risk stratification without prematurely guiding decisions on treatment limitations.

While the RAPID score should not be interpreted as a tool for individual-level decision-making regarding withdrawal of life-sustaining therapy, it may support structured risk communication, early clinical workflow stratification, and benchmarking in post-cardiac

arrest care. The availability of an online calculator further facilitates its potential integration into clinical workflows.

In summary, the RAPID score provides a pragmatic and early prognostic framework for OHCA patients undergoing targeted temperature management. By capturing key elements of cardiovascular, metabolic, and arrest-related injury shortly after admission, it complements existing prognostic approaches and may contribute to more individualized post-cardiac arrest care. Although the RAPID score demonstrated good discriminatory performance and stable internal validation characteristics, external validation in independent multicenter cohorts is still required before routine clinical implementation.

5.3. Long-term Cardiovascular Follow-Up and Device-Based Remote Monitoring in High-Risk Cardiac Patients

In the third study, the investigated cohort did not specifically consist of survivors of sudden cardiac arrest, but rather a broader high-risk heart failure population treated with cardiac implantable electronic devices and followed using remote monitoring strategies. Nevertheless, these patients share several clinically relevant characteristics with post-cardiac arrest populations, including increased arrhythmic risk, progression of heart failure, and the need for structured long-term cardiovascular follow-up and multidisciplinary care. The COVID-19 pandemic profoundly reshaped healthcare systems, particularly through the postponement of non-urgent outpatient care and the prioritization of hospital capacity for acute cases (115). Within this context, telecardiology and remote monitoring emerged as potential tools to maintain continuity of care for patients with chronic heart failure. Previous randomized and observational studies have suggested that remote monitoring (RM) may improve clinical outcomes, including mortality, in selected device-treated heart failure populations, as exemplified by the IN-TIME trial, where daily RM was associated with a significant reduction in one-year mortality compared with standard follow-up and decrease hospitalization due to worsening heart failure (80).

In the present study, the impact of the pandemic on the safety and effectiveness of RM was assessed using complementary approaches, including outpatient visit frequency, device-derived parameters, and patient-reported outcomes. A marked reduction in in-office follow-up visits was observed following the outbreak of the pandemic, reflecting

the immediate consequences of lockdown measures and healthcare reorganization. Importantly, this decline in personal visits was not accompanied by an increase in acute heart failure events, suggesting that RM-based follow-up was able to preserve short-term clinical stability in this high-risk population.

These findings are partly consistent with earlier reports. Ziacchi et al. described an increase in RM alerts during lockdown periods, interpreted as a potential signal of heart failure deterioration (116). In contrast, our data did not demonstrate a parallel rise in clinically overt acute decompensation, a discrepancy that may be explained by differences in study design, event definitions, and statistical power. Similarly, Zorzi and colleagues reported no increase in arrhythmic events or mortality among remotely monitored ICD patients during the pandemic compared with the preceding year (117). Taken together, these observations suggest that while RM systems may detect subtle physiological changes, the reduction in outpatient clinic visits during lockdown did not necessarily translate into worsened short-term hard clinical outcomes.

Analysis of device-derived parameters revealed overall stability across the studied periods, with the notable exception of patient activity. Physical activity increased following the easing of restrictions, particularly among patients younger than 70 years. This finding contrasts with several reports describing reduced activity levels during lockdown among heart failure patients (83, 117, 118, 119). However, most prior studies focused exclusively on the lockdown period and did not evaluate post-lockdown recovery. Our results align more closely with observations by Cunha et al., who demonstrated heterogeneous post-lockdown recovery patterns, with only a subset of patients returning to or exceeding baseline activity levels (120). The observed increase in activity after restrictions may reflect behavioral adaptation, increased health awareness, or a rebound effect following prolonged confinement (121). Given the established prognostic importance of physical activity in heart failure populations, these findings highlight the potential of RM to capture clinically meaningful lifestyle changes beyond traditional clinical endpoints (120).

While heart failure symptoms and disease-specific quality of life remained largely unchanged, a substantial deterioration in psychological well-being was observed during the lockdown period. Patients reported significantly higher levels of anxiety and

depression, as well as greater impairment in social functioning. These findings are consistent with studies conducted during the pandemic that identified heightened psychological distress among patients with cardiovascular disease, irrespective of RM utilization (122, 123). Importantly, the magnitude of psychological burden observed in our cohort underscores that RM, while effective in maintaining somatic stability, does not mitigate the broader psychosocial consequences of prolonged isolation and pandemic-related stressors. Prior work has emphasized the role of physical activity and psychosocial support as modifiable factors influencing mental health and cardiovascular risk during periods of societal stress (124).

In summary, our findings indicate that remote monitoring enabled continuity of care and preserved short-term clinical stability in CHF patients during the COVID-19 pandemic, despite a substantial reduction in outpatient clinic follow-up visits. At the same time, significant changes in physical activity patterns and psychological well-being highlight dimensions of patient care that extend beyond traditional clinical endpoints. These results support the integration of RM into routine heart failure management while emphasizing the need for complementary strategies addressing mental health and lifestyle factors, particularly during periods of healthcare system disruption.

5.4. Limitations

Several limitations of the present dissertation should be acknowledged. First, two of the analyses were conducted in single-center cohorts, which may limit the generalizability of the findings. As a tertiary cardiovascular referral center with a high-volume interventional cardiology service, our institution manages a selected OHCA population characterized by a relatively high proportion of cardiac-origin arrests, ST-segment elevation myocardial infarction, and shockable initial rhythms. This referral pattern may introduce selection bias in the prognostic analyses.

Second, in the environmental epidemiology analysis, temperature exposure was assigned using regional meteorological data, which may not fully reflect individual-level exposure or microclimatic conditions. Although models were adjusted for major temporal confounders, information on other environmental factors such as air pollution or infectious activity was not available. In addition, the number of extreme temperature events during the study period was relatively limited, resulting in less precise estimates

in some subgroup analyses. Furthermore, the DLNM was evaluated across a 21-day lag window to capture both the immediate effects of heat exposure and the delayed effects of cold exposure. Shorter lag windows (3 and 7 days) were also explored during model development; however, the 21-day window was retained for the primary analysis because previous studies have demonstrated that cold-related cardiovascular effects may emerge several days after exposure and persist for up to several weeks. Therefore, a longer lag structure was considered more appropriate for capturing the full temporal pattern of temperature-related OHCA risk. Incidence rate ratios represent relative measures of association and therefore do not directly quantify the absolute excess number of OHCA events attributable to extreme temperatures. Although absolute event estimates may provide additional public health perspective, the primary aim of the present study was to investigate relative population-level associations between extreme temperature exposures and OHCA occurrence.

Third, the RAPID score study was retrospective and based on a relatively small sample size. As this was a retrospective observational study, several variables contained incomplete data, predominantly related to prehospital parameters due to incomplete EMS documentation during the early study period. Therefore, patients with more than 10% missing data across the evaluated parameters were excluded from the final modelling cohort, which may have introduced a degree of selection bias. Although internal validation was performed, external validation in independent, multicenter cohorts is required before broader clinical implementation. Moreover, the model was designed to estimate early mortality risk and does not directly assess neurological outcomes or identify patients who may benefit from specific therapeutic interventions.

Finally, the device-based follow-up analysis was also retrospective and conducted during the COVID-19 pandemic, a period associated with substantial changes in healthcare delivery and patient behavior, which may have influenced healthcare utilization, patient activity levels, and symptom reporting. These factors should be considered when interpreting the findings. Another limitation is that the third study investigated a broader high-risk cardiovascular population with cardiac implantable electronic devices rather than specifically survivors of sudden cardiac arrest. Therefore, conclusions regarding

long-term follow-up and remote monitoring should be interpreted within this clinical context.

6. Conclusion

Extreme temperatures were independently associated with an increased incidence of out-of-hospital cardiac arrest in the Hungarian population. Heat exposure was associated with an immediate but short-lived increase in risk, whereas cold exposure resulted in a delayed and more sustained excess risk, indicating distinct temporal risk patterns for heat and cold. Following cardiac arrest, early outcome was shown to be predictable using a limited set of routinely available clinical parameters in patients treated with targeted temperature management. With the development of the RAPID score, heart rate, age, arterial pH, initial rhythm, and right ventricular end-diastolic diameter were identified as independent predictors of 30-day mortality within the first 12 hours of intensive care admission, supporting the feasibility of early and objective risk stratification in the post-resuscitation phase. Beyond the acute phase, long-term clinical stability in high-risk cardiac patients with implantable devices could be maintained through remote monitoring, even with a substantial reduction in in-person follow-up. Heart failure-related device parameters, arrhythmic events (including atrial high-rate episodes and ventricular tachycardia and ventricular fibrillation), acute decompensation rates, and patient-reported symptoms remained unchanged, confirming that telemonitoring can safely support continuity of care in vulnerable populations.

7. Summary

The dissertation investigates multiple clinically related aspects of sudden cardiac arrest and advanced cardiovascular care. The first two studies focus specifically on population-level vulnerability to out-of-hospital cardiac arrest and early post-resuscitation intensive care management, while the third study addresses long-term follow-up and remote monitoring in a broader high-risk heart failure population treated with cardiac implantable electronic devices. Together, these studies provide a comprehensive perspective on factors influencing outcomes in critically ill cardiovascular patients.

The population-based analysis demonstrated that both extreme heat and extreme cold are associated with an increased incidence of out-of-hospital cardiac arrest in the Hungarian population. The temporal patterns of these associations differed, with heat-related effects appearing shortly after exposure and cold-related effects showing a more delayed and prolonged course. These findings support the concept that temperature-related risk is heterogeneous and context dependent, and they add region-specific evidence from a continental climate setting to the existing literature.

In the acute post-resuscitation phase, the RAPID score was developed and internally validated as an early risk stratification tool for patients treated with targeted temperature management after cardiac arrest. The model relies on routinely available clinical parameters obtained during the first hours of intensive care and demonstrated good discriminatory performance. The results suggest that early, post-cardiac arrest-specific risk assessment based on simple clinical variables is feasible and may complement clinical judgment during the initial phase of intensive care.

The third study focused on long-term follow-up and remote monitoring in patients with chronic heart failure and implantable cardiac devices. During a period of restricted access to in-person care, remote monitoring allowed continuity of follow-up without deterioration in device-derived heart failure parameters or patient-reported symptoms. These findings indicate that telecardiology can provide a reliable adjunct to conventional outpatient care and may help maintain clinical stability in high-risk patients under constrained healthcare conditions.

Overall, the results of this dissertation underscore that sudden cardiac arrest should not be viewed as an isolated event but as a condition with population-level determinants, an acute critical care phase, and long-term cardiological consequences.

8. References

1. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M, Group ESCSD. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43(40):3997-4126.

2. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt LL, Goldberger ZD, Gopinathannair R, Gorenek B, Hess PL, Hlatky M, Hogan G, Ibeh C, Indik JH, Kido K, Kusumoto F, Link MS, Linta KT, Marcus GM, McCarthy PM, Patel N, Patton KK, Perez MV, Piccini JP, Russo AM, Sanders P, Streur MM, Thomas KL, Times S, Tisdale JE, Valente AM, Van Wagoner DR, Peer Review Committee M. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(1):e1-e156.

3. Rajan D, Zorner CR, Hansen ML, Tfelt-Hansen J. Arrhythmias and Sudden Death: What is New in Hypertrophic Cardiomyopathy? Card Fail Rev. 2025;11:e08.

4. Bray JE, Grasner JT, Nolan JP, Iwami T, Ong MEH, Finn J, McNally B, Nehme Z, Sasson C, Tijssen J, Lim SL, Tjelmeland I, Wnent J, Dicker B, Nishiyama C, Doherty Z, Welsford M, Perkins GD, International Liaison Committee on R. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: 2024 Update of the Utstein Out-of-Hospital Cardiac Arrest Registry Template. Circulation. 2024;150(9):e203-e23.

5. Yan S, Gan Y, Jiang N, Wang R, Chen Y, Luo Z, Zong Q, Chen S, Ly C. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care. 2020;24(1):61.

6. Schwaiger D, Krosbacher A, Eckhardt C, Schausberger L, Baubin M, Rajsic S. Out-of-hospital cardiac arrest: A 10-year analysis of survival and neurological outcomes. Heart Lung. 2025;73:1-8.

7. Gräsner JT, Wnent J, Lefering R, Herlitz J, Masterson S, Maurer H, Perkins GD, Ortiz FR, Tjelmeland IBM, Kamishi D, Moertl D, Mols P, Alihodzic H, Ioannides M, Truhlář A, Baert V, Nikolaou N, Molnar N, Jonsson BS, Semeraro F, Krikscionaitiene A, Clarens C, Giordimaina C, Stieglis R, Zadlo A, Correia VH, Cimpoesu D, Raffay V, Trenkler S, Strnad M, Ruiz JI, Strømsøe A, Wilmes A, Booth S, Bossaert L. European registry of cardiac arrest study THREE (EuReCa-THREE) - EMS response time influence on outcome in Europe. Resuscitation. 2025. Epub ahead of print. doi:10.1016/j.resuscitation.2025.110704.

8. Nagy B, Kiss B, Fülöp GÁ, Zima E. Out-of-Hospital Cardiac Arrest in General Population and Sudden Cardiac Death in Athletes. In: Zima E, editor. Cardiac Arrhythmias - Translational Approach from Pathophysiology to Advanced Care. London: IntechOpen; 2022. p. 75-87. doi:10.5772/intechopen.101813.

9. Yoshimura S, Tseng ZH, Yamada T, Nakao S, Yoshiya K, Park C, Nishimura T, Ishibe T, Yamakawa K, Kiguchi T, Kishimoto M, Ninomiya K, Ito Y, Sogabe T, Morooka T, Sakamoto H, Hironaka Y, Onoe A, Matsuyama T, Okada Y, Matsui S, Nishioka N, Kimata S, Kawai S, Makino Y, Zha L, Kiyohara K, Kitamura T, Iwami T, Investigators CSG. Underlying Cause of Out-of-Hospital Cardiac Arrests in Japan in Survivors Versus Nonsurvivors. J Am Heart Assoc. 2025;14(9):e036968.

10. Radu I, Farcas AO, Nyulas V, Radu CC, Brinzaniuc K. Sudden cardiac death—etiology, risk factors and demographic characteristics: an extensive study of 1618 forensic autopsies. Diseases. 2024;12(8):168.

11. Marimpouy N, Guilbeau-Frugier C, Ramirez A, Beneyto M, Delmas C, Biendel C, Cherbi M, Foltran D, Mondoly P, Timnou Bekouti J, Ferrieres J, Telmon N, Bongard V, Delasnerie H, Rollin A, Maury P. Current causes of sudden death in large populations: differences between resuscitated patients and autopsied cases. Eur Heart J Open. 2025;5(5):oeaf125.

12. Marijon E, Narayanan K, Smith K, Barra S, Basso C, Blom MT, Crotti L, D'Avila A, Deo R, Dumas F, Dzudie A, Farrugia A, Greeley K, Hindricks G, Hua W, Ingles J, Iwami T, Junttila J, Koster RW, Le Polain De Waroux JB, Olasveengen TM, Ong MEH, Papadakis M, Sasson C, Shin SD, Tse HF, Tseng Z, Van Der Werf C, Folke F, Albert CM,

Winkel BG. The Lancet Commission to reduce the global burden of sudden cardiac death: a call for multidisciplinary action. Lancet. 2023;402(10405):883-936.

13. Lagebrant A, Sandroni C, Nolan JP, Belohlavek J, Cariou A, Carrai R, Dankiewicz J, Grejs AM, Grippo A, Hassager C, Horn J, Haenggi M, Jakobsen JC, Keeble TR, Kirkegaard H, Kjaergaard J, Kuiper MA, Lee BK, Lee DH, Levin H, Lilja G, Lundin A, Nielsen N, Oh SH, Park KN, Pellis T, Robba C, Rylander C, Ryu SJ, Saxena M, Scarpino M, Schrag C, Stammet P, Storm C, Taccone FS, Thomas M, Westhall E, Wise MP, Youn CS, Young P, Cronberg T, Moseby-Knappe M. Prediction of good functional outcome decreases diagnostic uncertainty in unconscious survivors after out-of-hospital cardiac arrest. Resuscitation. 2025;214:110686.

14. Jaiswal V, Kumar D, Mashkoor Y, Latif F, Kanagala SG, Halder A, Jaiswal A, Bandyopadhyay D, Hajra A, Joshi A, Aronow WS, Fonarow GC. Demographics and Trends of Sudden Cardiac Death-Related Mortality in the United States, 1999 to 2022. J Am Heart Assoc. 2025;14(18):e040340.

15. Zimmerman DS, Tan HL. Epidemiology and risk factors of sudden cardiac arrest. Curr Opin Crit Care. 2021;27(6):613-6.

16. Mittleman MA, Mostofsky E. Physical, psychological and chemical triggers of acute cardiovascular events: preventive strategies. Circulation. 2011;124(3):346-54.

17. Blaustein JR, Quisel MJ, Hamburg NM, Wittkopp S. Environmental Impacts on Cardiovascular Health and Biology: An Overview. Circ Res. 2024;134(9):1048-60.

18. Burger M, Ristau P, Bohn A, Fischer M, Tjelmeland IBM, Seewald S, Grasner JT, Wnent J. Air temperature and humidity impact out-of-hospital-cardiac-arrests in Germany: A 10-year cohort study from the German Resuscitation Registry. Resusc Plus. 2024;20:100750.

19. Khan L, Kawano T, Hutton J, Asamoah-Boaheng M, Scheuermeyer FX, Christian M, Baranowski L, Barbic D, Christenson J, Grunau B. The association of extreme environmental heat with incidence and outcomes of out-of-hospital cardiac arrest in British Columbia: A time series analysis. Resusc Plus. 2024;17:100560.

20. Wang L, Liu J, Yin P, Gao Y, Jiang Y, Kan H, Zhou M, Ao H, Chen R. Mortality risk and burden of sudden cardiac arrest associated with hot nights, heatwaves, cold spells, and non-optimum temperatures in 0.88 million patients: An individual-level case-crossover study. Sci Total Environ. 2024;949:175208.

21. Onozuka D, Hagihara A. Extreme temperature and out-of-hospital cardiac arrest in Japan: A nationwide, retrospective, observational study. Sci Total Environ. 2017;575:258-64.

22. Yu X, Liu J, Yin P, Gao Y, He C, Kan H, Zhou M, Huo Y, Chen R. Nonlinear relation between cardiac mortality and excess temperature in heatwaves: exposure response in 2.39 million patients. J Am Coll Cardiol. 2025 Mar 13:S0735-1097(25)00339-0.

23. Galli GM, Kaviyarasu A, Agarwal S, Counts CR, Scquizzato T, Yang B, Owyang CG, Coute R, Orlob S, Shepard L, Halablab S, Horowitz J, Perman S, Morgan R, Grossestreuer A, Vine J, Johnson N, Andrea L, Moskowitz A, Abella B, Dezfulian C, Farooqi WH, Teran F. The Latest in Resuscitation Research: Highlights From the 2024 American Heart Association's Resuscitation Science Symposium. J Am Heart Assoc. 2025;14(19):e043181.

24. Hirsch KG, Amorim E, Coppler PJ, Drennan IR, Elliott A, Gordon AJ, Jentzer JC, Johnson NJ, Moskowitz A, Mumma BE, Presciutti AM, Rodriguez AJ, Yen AF, Rittenberger JC. Part 11: Post-Cardiac Arrest Care: 2025 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2025;152(16_suppl_2):S673-S718.

25. Sorini Dini C, Geraci G, Valente S, Tizzani E, Sacco A, Grimaldi M, Colivicchi F, Oliva F, a nome del club delle UA. [Post-cardiac arrest syndrome: definition, pathophysiology, and management]. G Ital Cardiol (Rome). 2025;26(7):488-99.

26. Yao Z, Zhao Y, Lu L, Li Y, Yu Z. Extracerebral multiple organ dysfunction and interactions with brain injury after cardiac arrest. Resusc Plus. 2024;19:100719.

27. Donoso-Trenado V, Otero-Garcia O, Lopez-Vilella R, de la Fuente Lopez P, Martinez-Sole J, Yebra-Pimentel Brea C, Guerrero-Cervera B, Adarraga Gomez J, Huelamo-Montoro S, Gallego-Latorre G, Garcia-Vega D, Gomez-Otero I, Martinez-Dolz

L, Gonzalez-Juanatey JR, Almenar Bonet L. Factors Predicting Myocardial Recovery After Hospitalization for De Novo Heart Failure with Reduced Left Ventricular Ejection Fraction: Results from the COMFE Registry. Biomedicines. 2025;13(5).

28. Borovac JA. Guideline-recommended medical therapy for de novo heart failure with reduced ejection fraction: be patient waiting for reverse remodelling. Eur Heart J. 2024;45(30):2782-4.

29. Leungsuwan K, Heier KR, Henderson O, Ayoub K, Alnabelsi T, Slade E, Gupta VA. Post cardiac arrest left ventricular ejection fraction associated with survival to discharge. Resusc Plus. 2024;19:100737.

30. Held EP, Reinier K, Chugh H, Uy-Evanado A, Jui J, Chugh SS. Recurrent Out-of-Hospital Sudden Cardiac Arrest: Prevalence and Clinical Factors. Circ Arrhythm Electrophysiol. 2022;15(12):e011018.

31. Lazzarin T, Tonon CR, Martins D, Favero EL Jr, Baumgratz TD, Pereira FWL, Pinheiro VR, Ballarin RS, Queiroz DAR, Azevedo PS, Polegato BF, Okoshi MP, Zornoff L, Rupp de Paiva SA, Minicucci MF. Post-cardiac arrest: mechanisms, management, and future perspectives. J Clin Med. 2022;12(1):259.

32. Alahmad B, Khraishah H, Roye D, Vicedo-Cabrera AM, Guo Y, Papatheodorou SI, Achilleos S, Acquaotta F, Armstrong B, Bell ML, Pan SC, de Sousa Zanotti Stagliorio Coelho M, Colistro V, Dang TN, Van Dung D, De' Donato FK, Entezari A, Guo YL, Hashizume M, Honda Y, Indermitte E, Iniguez C, Jaakkola JJK, Kim H, Lavigne E, Lee W, Li S, Madureira J, Mayvaneh F, Orru H, Overcenco A, Ragettli MS, Ryti NRI, Saldiva PHN, Scovronick N, Seposo X, Sera F, Silva SP, Stafoggia M, Tobias A, Garshick E, Bernstein AS, Zanobetti A, Schwartz J, Gasparrini A, Koutrakis P. Associations Between Extreme Temperatures and Cardiovascular Cause-Specific Mortality: Results From 27 Countries. Circulation. 2023;147(1):35-46.

33. Munzel T, Khraishah H, Schneider A, Lelieveld J, Daiber A, Rajagopalan S. Challenges posed by climate hazards to cardiovascular health and cardiac intensive care: implications for mitigation and adaptation. Eur Heart J Acute Cardiovasc Care. 2024;13(10):731-44.

34. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. Am J Physiol Heart Circ Physiol. 2015;309(11):H1793-812.

35. Borchert W, Grady ST, Chen J, DeVille NV, Roscoe C, Chen F, Mita C, Holland I, Wilt GE, Hu CR, Mehta U, Nethery RC, Albert CM, Laden F, Hart JE. Air Pollution and Temperature: a Systematic Review of Ubiquitous Environmental Exposures and Sudden Cardiac Death. Curr Environ Health Rep. 2023;10(4):490-500.

36. Wu Q, Yang M, Wu K, Su H, Huang C, Xu Z, Ho HC, Zheng H, Zhang W, Tao J, Dang TAT, Hossain MZ, Khan MA, Bogale D, Cheng J. Abnormal ambient temperature change increases the risk of out-of-hospital cardiac arrest: A systematic review and meta-analysis of exposure types, risk, and vulnerable populations. Sci Total Environ. 2023;861:160554.

37. Kranc H, Novack V, Shtein A, Sherman R, Novack L. Extreme temperature and out-of-hospital-cardiac-arrest. Nationwide study in a hot climate country. Environ Health. 2021;20(1):38.

38. Kang SH, Oh IY, Heo J, Lee H, Kim J, Lim WH, Cho Y, Choi EK, Yi SM, Sang do S, Kim H, Youn TJ, Chae IH, Oh S. Heat, heat waves, and out-of-hospital cardiac arrest. Int J Cardiol. 2016;221:232-7.

39. Yamazaki S, Michikawa T. Association between high and low ambient temperature and out-of-hospital cardiac arrest with cardiac etiology in Japan: a case-crossover study. Environ Health Prev Med. 2017;22(1):60.

40. Liu J, Lv C, Zheng J, Pan C, Zhang G, Tan H, Ma Y, Zhu Y, Han X, Li C, Yan S, Ma J, Zhang J, Wang C, Bian Y, Cheng K, Liu R, Hou Y, Chen Q, Zhang X, Chen Y, Chen R, Xu F. The impact of non-optimum temperatures, heatwaves and cold spells on out-of-hospital cardiac arrest onset in a changing climate in China: a multi-center, time-stratified, case-crossover study. Lancet Reg Health West Pac. 2023;36:100778.

41. Spinoni J, Szalai S, Szentimrey T, Lakatos M, Bihari Z, Nagy A, Németh Á, Kovács T, Mihic D, Dacic M, Petrovic P, Kržič A, Hiebl J, Auer I, Milkovic J, Štepánek P, Zahradnícek P, Kilar P, Limanowka D, Pyrc R, Cheval S, Birsan M - V, Dumitrescu A, Deak G, Matei M, Antolovic I, Nejedlík P, Štastný P, Kajaba P, Bochnícek O, Galo D, Mikulová K, Nabyvanets Y, Skrynyk O, Krakovska S, Gnatiuk

N, Tolasz R, Antofie T, Vogt J. Climate of the Carpathian Region in the period961-2010: climatologies and trends of0 variables. Int J Climatol. 2015;35(7):1322-1344.

42. Spinoni J, Lakatos M, Szentimrey T, Bihari Z, Szalai S, Vogt J, Antofie TE. Heat and cold waves trends in the Carpathian Region from 1961 to 2010. Int J Climatol. 2015;35(14):4197-4209. doi:10.1002/joc.4279.

43. Magyar Meteorológiai Szolgáltató Nonprofit Zrt. Éghajlati körzetek változása [Internet]. [cited 2026 Jan 26]. Available from: https://www.met.hu/eghajlat/eghajlatvaltozas/megfigyelt_hazai_valtozasok/eghajlati_korzetek_valtozasa/index.php

44. Nolan JP, Sandroni C, Cariou A, Cronberg T, D'Arrigo S, Haywood K, Hoedemaekers A, Lilja G, Nikolaou N, Olasveengen TM, Robba C, Skrifvars MB, Swindell P, Soar J. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2025 Post-Resuscitation Care. Resuscitation. 2025;215 Suppl 1:110809.

45. Greif R, Lauridsen KG, Djarv T, Ek JE, Monnelly V, Monsieurs KG, Nikolaou N, Olasveengen TM, Semeraro F, Spartinou A, Yeung J, Baldi E, Biarent D, Djakow J, van Gils M, van Goor S, Grasner JT, Hogeveen M, Karageorgos V, Lott C, Madar J, Nabecker S, de Raad T, Raffay V, Rogers J, Sandroni C, Schnaubelt S, Smyth MA, Soar J, Wittig J, Perkins GD, Nolan JP, European Resuscitation Council Guidelines Collaborator G. European Resuscitation Council Guidelines 2025 Executive Summary. Resuscitation. 2025;215 Suppl 1:110770.

46. Sandroni C, Cronberg T, Sekhon M. Brain injury after cardiac arrest: pathophysiology, treatment, and prognosis. Intensive Care Med. 2021;47(12):1393-414.

47. Topjian AA, de Caen A, Wainwright MS, Abella BS, Abend NS, Atkins DL, Bembea MM, Fink EL, Guerguerian AM, Haskell SE, Kilgannon JH, Lasa JJ, Hazinski MF. Pediatric Post-Cardiac Arrest Care: A Scientific Statement From the American Heart Association. Circulation. 2019;140(6):e194-e233.

48. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549-56.

49. Taccone FS, Lascarrou JB, Skrifvars MB. Targeted temperature management and cardiac arrest after the TTM-2 study. Crit Care. 2021;25(1):275.

50. Fernandez Hernandez S, Barlow B, Pertsovskaya V, Maciel CB. Temperature Control After Cardiac Arrest: A Narrative Review. Adv Ther. 2023;40(5):2097-115.

51. Sandroni C, Natalini D, Nolan JP. Temperature control after cardiac arrest. Crit Care. 2022;26(1):361.

52. Nolan JP, Sandroni C, Cariou A, Cronberg T, D'Arrigo S, Haywood K, Hoedemaekers A, Lilja G, Nikolaou N, Olasveengen TM, Robba C, Skrifvars MB, Swindell P, Soar J. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2025: post-resuscitation care. Intensive Care Med. 2025;51(12):2213-88.

53. Pilecky D, Szudi G, Kovacs E, Jenei Z, Geller L, Heltai K, Molnar L, Barczi G, Becker D, Merkely B, Zima E. [The role of therapeutic hypothermia in post-resuscitation care - review of the literature and personal experience]. Orv Hetil. 2016;157(16):611-7.

54. Schock RB, Janata A, Peacock WF, Deal NS, Kalra S, Sterz F. Time to Cooling Is Associated with Resuscitation Outcomes. Ther Hypothermia Temp Manag. 2016;6(4):208-17.

55. Guluma KZ, Hemmen TM, Olsen SE, Rapp KS, Lyden PD. A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: methodology. Acad Emerg Med. 2006;13(8):820-7.

56. Calabro L, Bougouin W, Cariou A, De Fazio C, Skrifvars M, Soreide E, Creteur J, Kirkegaard H, Legriel S, Lascarrou JB, Megarbane B, Deye N, Taccone FS. Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: a systematic review and meta-analysis. Crit Care. 2019;23(1):285.

57. Finley Caulfield A, Rachabattula S, Eyngorn I, Hamilton SA, Kalimuthu R, Hsia AW, Lansberg MG, Venkatasubramanian C, Baumann JJ, Buckwalter MS, Kumar MA, Castle JS, Wijman CA. A comparison of cooling techniques to treat cardiac arrest patients with hypothermia. Stroke Res Treat. 2011;2011:690506.

58. Jung YS, Kim KS, Suh GJ, Cho JH. Comparison between Gel Pad Cooling Device and Water Blanket during Target Temperature Management in Cardiac Arrest Patients. Acute Crit Care. 2018;33(4):246-51.

59. Sonder P, Janssens GN, Beishuizen A, Henry CL, Rittenberger JC, Callaway CW, Dezfulian C, Polderman KH. Efficacy of different cooling technologies for therapeutic temperature management: A prospective intervention study. Resuscitation. 2018;124:14-20.

60. Zeiner A, Holzer M, Sterz F, Behringer W, Schorkhuber W, Mullner M, Frass M, Siostrzonek P, Ratheiser K, Kaff A, Laggner AN. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke. 2000;31(1):86-94.

61. Shin M, Fujita M, Hifumi T, Koga Y, Yagi T, Nakahara T, Todani M, Kaneda K, Tsuruta R. Rapid rewarming rate associated with favorable neurological outcomes in patients with post-cardiac arrest syndrome patients treated with targeted temperature management. Acute Med Surg. 2023;10(1):e897.

62. Tirkkonen J, Skrifvars MB. Change of target temperature from 36°C to strict fever avoidance only in comatose cardiac arrest survivors: a before-and-after study. Resuscitation. 2023;188:109796.

63. Staudacher DL, Heine L, Rilinger J, Maier A, Rottmann FA, Zotzmann V, Kaier K, Biever PM, Supady A, Westermann D, Wengenmayer T, Jäckel M. Impact of sedation depth on neurological outcome in post-cardiac arrest patients — a retrospective cohort study. Resuscitation. 2024 Dec;205:110456.2024.110456. Epub 2024 Dec 2.

64. Matsuda J, Kato S, Yano H, Nitta G, Kono T, Ikenouchi T, Murata K, Kanoh M, Inamura Y, Takamiya T, Negi K, Sato A, Yamato T, Inaba O, Morita H, Matsumura Y, Nitta J, Yonetsu T. The Sequential Organ Failure Assessment (SOFA) score predicts mortality and neurological outcome in patients with post-cardiac arrest syndrome. J Cardiol. 2020;76(3):295-302.

65. Yoon JC, Kim YJ, Lee YJ, Ryoo SM, Sohn CH, Seo DW, Lee YS, Lee JH, Lim KS, Kim WY. Serial evaluation of SOFA and APACHE II scores to predict neurologic

outcomes of out-of-hospital cardiac arrest survivors with targeted temperature management. PLoS One. 2018;13(4):e0195628.

66. Chen C-H, Wang C-J, Wang I-T, Yang S-H, Wang Y-H, Lin C-Y. Does one size fit all? External validation of the rCAST score to predict the hospital outcomes of post-cardiac arrest patients receiving targeted temperature management. J Clin Med. 2022;12(1):242.

67. Choi JY, Jang JH, Lim YS, Jang JY, Lee G, Yang HJ, Cho JS, Hyun SY. Performance on the APACHE II, SAPS II, SOFA and the OHCA score of post-cardiac arrest patients treated with therapeutic hypothermia. PLoS One. 2018;13(5):e0196197.

68. Isenschmid C, Luescher T, Rasiah R, Kalt J, Tondorf T, Gamp M, Becker C, Tisljar K, Sutter R, Schuetz P, Hochstrasser S, Metzger K, Marsch S, Hunziker S. Performance of clinical risk scores to predict mortality and neurological outcome in cardiac arrest patients. Resuscitation. 2019;136:21-9.

69. Nishikimi M, Ogura T, Nishida K, Takahashi K, Nakamura M, Matsui S, Matsuda N, Iwami T. External validation of a risk classification at the emergency department of post-cardiac arrest syndrome patients undergoing targeted temperature management. Resuscitation. 2019;140:135-41.

70. Maupain C, Bougouin W, Lamhaut L, Deye N, Diehl JL, Geri G, Perier MC, Beganton F, Marijon E, Jouven X, Cariou A, Dumas F. The CAHP (Cardiac Arrest Hospital Prognosis) score: a tool for risk stratification after out-of-hospital cardiac arrest. Eur Heart J. 2016;37(42):3222-8.

71. Coppler PJ, Elmer J, Calderon L, Sabedra A, Doshi AA, Callaway CW, Rittenberger JC, Dezfulian C, Post Cardiac Arrest S. Validation of the Pittsburgh Cardiac Arrest Category illness severity score. Resuscitation. 2015;89:86-92.

72. Granger CB, Hansen CM. Predicting outcome in cardiac arrest: some progress, but more work needed. Eur Heart J. 2020;41(47):4518-20.

73. Lim HJ, Ro YS, Kim KH, Park JH, Hong KJ, Song KJ, Shin SD. The ED-PLANN score: a simple risk stratification tool for out-of-hospital cardiac arrests derived from emergency departments in Korea. J Clin Med. 2021;10(1):119.

74. Martinell L, Nielsen N, Herlitz J, Karlsson T, Horn J, Wise MP, Undén J, Rylander C. Early predictors of poor outcome after out-of-hospital cardiac arrest. Crit Care. 2017;21(1):96.

75. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Skibelund AK, Group ESCSD. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44(37):3627-39.

76. Raphalen JH, Soumagnac T, Delord M, Bougouin W, Georges JL, Paul M, Legriel S. Long-term heart function in cardiac-arrest survivors. Resusc Plus. 2023;16:100481.

77. Ortuno S, Bougouin W, Voicu S, Paul M, Lascarrou JB, Benghanem S, Dumas F, Beganton F, Karam N, Marijon E, Jouven X, Cariou A, Aissaoui N. Long-term major events after hospital discharge for out-of-hospital cardiac arrest. Ann Intensive Care. 2024;14(1):144.

78. Gupta A, Gupta A, Saba S. Change in myocardial function after resuscitated sudden cardiac arrest and its impact on long-term mortality and defibrillator implantation. Indian Pacing Electrophysiol J. 2019;19(4):150-4.

79. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, Barrabés JA, Boriani G, Braunschweig F, Brignole M, Burri H, Coats AJS, Deharo JC, Delgado V, Diller GP, Israel CW, Keren A, Knops RE, Kotecha D, Leclercq C, Merkely B, Starck C, Thylén I, Tolosana JM; Group ESCSD. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021;42(35):3427-520.

80. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, Brachmann J, Lewalter T, Goette A, Block M, Kautzner J, Sack S, Husser D, Piorkowski C, Sogaard P, group* I-Ts. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. Lancet. 2014;384(9943):583-90.

81. Klersy C, Boriani G, De Silvestri A, Mairesse GH, Braunschweig F, Scotti V, Balduini A, Cowie MR, Leyva F, Health Economics Committee of the European Heart

Rhythm A. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: a meta-analysis of randomized controlled trials in patients with heart failure. Eur J Heart Fail. 2016;18(2):195-204.

82. Zima E, Duray GZ, Kiss B, Vámos M, Sághy L, Földesi C, Kardos A, Tahin T, Clemens M, Csanádi Z, Merkely BP, Gellér L. Implantation rates of cardiac implantable electronic devices in Hungary between 2017 and 2020. Cardiologia Hungarica. 2021;51(4):246-253.

83. Bertagnin E, Greco A, Bottaro G, Zappulla P, Romanazzi I, Russo MD, Lo Presti M, Valenti N, Sollano G, Calvi V. Remote monitoring for heart failure management during COVID-19 pandemic. Int J Cardiol Heart Vasc. 2021;32:100724.

84. Varma N, Braunschweig F, Burri H, Hindricks G, Linz D, Michowitz Y, Ricci RP, Nielsen JC. Remote monitoring of cardiac implantable electronic devices and disease management. Europace. 2023;25(9).

85. De Simone A, Leoni L, Luzi M, Amellone C, Stabile G, La Rocca V, Capucci A, D'Onofrio A, Ammendola E, Accardi F, Valsecchi S, Buja G. Remote monitoring improves outcome after ICD implantation: the clinical efficacy in the management of heart failure (EFFECT) study. Europace. 2015;17(8):1267-75.

86. Sokolski M, Kaluzna-Oleksy M, Tycinska A, Jankowska EA. Telemedicine in Heart Failure in the COVID-19 and Post-Pandemic Era: What Have We Learned? Biomedicines. 2023;11(8).

87. Richards-Belle A, Mouncey PR, Grieve RD, Harrison DA, Sadique MZ, Henry D, Whitman C, Camsooksai J, Gordon AC, Young JD, Rowan KM, Lamontagne F. Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension: Protocol for the 65 randomised clinical trial. J Intensive Care Soc. 2020;21(4):281-2.

88. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

89. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245-55.

90. Nagy B, Pál-Jakab Á, Kiss B, Morvai A, Sipos B, Pápai Gy, Csató G, Orbán G, Boussoussou N, Merkely B, Sótonyi P, Gerencsér A, Szilágyi B, Zima E. Influence of extreme temperatures on out-of-hospital cardiac arrest cases in Hungary: a national time-series analysis. Resuscitation Plus. 2025;27:101194.

91. Ahn C, Kim J, Kim W, Kim IY, Choi HY, Kim JG, Kim B, Moon S, Shin H, Lee J. Association of ambient temperature with the outcomes in witnessed out-of-hospital cardiac arrest patients: a population-based observational study. Sci Rep. 2019;9(1):13417.

92. Dear K, Wang Z. Climate and health: mortality attributable to heat and cold. Lancet. 2015;386(9991):320-2.

93. Cho EJ, Shin SD, Jeong S, Kwak YH, Suh GJ. The effect of atmosphere temperature on out-of-hospital cardiac arrest outcomes. Resuscitation. 2016;109:64-70.

94. Kovacs E, Jenei Z, Horvath A, Geller L, Szilagyi S, Kiraly A, Molnár L, Sótonyi P, Merkely B, Zima E. Physiologic effects of hypothermia. Orv Hetil. 2011;152(5):171-81.

95. Onozuka D, Hagihara A. Associations of day-to-day temperature change and diurnal temperature range with out-of-hospital cardiac arrest. Eur J Prev Cardiol. 2017;24(2):204-12.

96. Yang J, Ou CQ, Ding Y, Zhou YX, Chen PY. Daily temperature and mortality: a study of distributed lag non-linear effect and effect modification in Guangzhou. Environ Health. 2012;11:63.

97. D'Ippoliti D, Michelozzi P, Marino C, de'Donato F, Menne B, Katsouyanni K, Kirchmayer U, Analitis A, Medina-Ramón M, Paldy A, Atkinson R, Kovats S, Bisanti L, Schneider A, Lefranc A, Iñiguez C, Perucci CA. The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project. Environ Health. 2010;9:37.

98. Jarman AF, Mumma BE, Perman SM, Kotini-Shah P, McGregor AJ. When the Female Heart Stops: Sex and Gender Differences in Out-of-Hospital Cardiac Arrest Epidemiology and Resuscitation. Clin Ther. 2019;41(6):1013-9.

99. Miedel C, Jonsson M, Dragas M, Djarv T, Nordberg P, Rawshani A, Claesson A, Forsberg S, Nord A, Herlitz J, Riva G. Underlying reasons for sex difference in survival following out-of-hospital cardiac arrest: a mediation analysis. Europace. 2024;26(5).

100. Kyriazopoulou E, Karakike E, Ekmektzoglou K, Kyprianou M, Gkolfakis P, Chalkias A, Kouskouni E, Xanthos T. Sinus Bradycardia During Targeted Temperature Management: A Systematic Review and Meta-Analysis. Ther Hypothermia Temp Manag. 2020;10(1):17-26.

101. Oksanen T, Tiainen M, Vaahersalo J, Bendel S, Varpula T, Skrifvars M, Pettilä V, Wilkman E. Lower heart rate is associated with good one-year outcome in post-resuscitation patients. Resuscitation. 2018;128:112-8.

102. Thomsen JH, Nielsen N, Hassager C, Wanscher M, Pehrson S, Kober L, Bro-Jeppesen J, Søholm H, Winther-Jensen M, Pellis T, Kuiper M, Erlinge D, Friberg H, Kjaergaard J. Bradycardia During Targeted Temperature Management: An Early Marker of Lower Mortality and Favorable Neurologic Outcome in Comatose Out-of-Hospital Cardiac Arrest Patients. Crit Care Med. 2016;44(2):308-18.

103. Awad E, Humphries K, Grunau B, Besserer F, Christenson J. The effect of sex and age on return of spontaneous circulation and survival to hospital discharge in patients with out of hospital cardiac arrest: A retrospective analysis of a Canadian population. Resusc Plus. 2021;5:100084.

104. Yang BY, Coult J, Blackwood J, Kwok H, Rajah A, Goldenberg I, Sotoodehenia N, Harris JR, Kudenchuk PJ, Rea TD. Age, sex, and survival following ventricular fibrillation cardiac arrest: A mechanistic evaluation of the ECG waveform. Resuscitation. 2023;189:109891.

105. Patz T, Stelzig K, Pfeifer R, Pittl U, Thiele H, Busch HJ, Reinhard I, Wolfrum S. Age-associated outcomes after survived out-of-hospital cardiac arrest and subsequent target temperature management. Acta Anaesthesiol Scand. 2019;63(8):1079-88.

106. Lin CH, Yu SH, Chen CY, Huang FW, Chen WK, Shih HM. Early blood pH as an independent predictor of neurological outcome in patients with out-of-hospital cardiac arrest: A retrospective observational study. Medicine (Baltimore). 2021;100(17):e25724.

107. Park YS, Choi YH, Oh JH, Cho IS, Cha KC, Choi BS, You JS. Recovery from acute kidney injury as a potent predictor of survival and good neurological outcome at discharge after out-of-hospital cardiac arrest. Crit Care. 2019;23(1):256.

108. Jamme M, Ben Hadj Salem O, Guillemet L, Dupland P, Bougouin W, Charpentier J, Mira JP, Pene F, Dumas F, Cariou A, Geri G. Severe metabolic acidosis after out-of-hospital cardiac arrest: risk factors and association with outcome. Ann Intensive Care. 2018;8(1):62.

109. Jensen TH, Juhl-Olsen P, Nielsen BRR, Heiberg J, Duez CHV, Jeppesen AN, Frederiksen CA, Kirkegaard H, Grejs AM. Echocardiographic parameters during prolonged targeted temperature management in out-of-hospital cardiac arrest survivors to predict neurological outcome: a post hoc analysis of the TTH48 trial. Scand J Trauma Resusc Emerg Med. 2021;29(1):37.

110. Harrell FE, Jr., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med. 1984;3(2):143-52.

111. Pareek N, Kordis P, Beckley-Hoelscher N, Pimenta D, Kocjancic ST, Jazbec A, Nevett J, Fothergill R, Kalra S, Lockie T, Shah AM, Byrne J, Noc M, MacCarthy P. A practical risk score for early prediction of neurological outcome after out-of-hospital cardiac arrest: MIRACLE2. Eur Heart J. 2020;41(47):4508-17.

112. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-31.

113. Nishikimi M, Matsuda N, Matsui K, Takahashi K, Ejima T, Liu K, Ogura T, Higashi M, Umino H, Makishi G, Numaguchi A, Matsushima S, Tokuyama H, Nakamura M, Matsui S. A novel scoring system for predicting the neurologic prognosis prior to the initiation of induced hypothermia in cases of post-cardiac arrest syndrome: the CAST score. Scand J Trauma Resusc Emerg Med. 2017;25(1):49.

114. Blatter R, Amacher SA, Bohren C, Becker C, Beck K, Gross S, Tisljar K, Sutter R, Marsch S, Hunziker S. Comparison of different clinical risk scores to predict long-term survival and neurological outcome in adults after cardiac arrest: results from a prospective cohort study. Ann Intensive Care. 2022;12(1):77.

115. McGinlay M, Straw S, Jagger J, Nouri B, Gierula J, Witte KK. Impact of the COVID-19 pandemic on the management of chronic heart failure. Rev Cardiovasc Med. 2021;22(2):271-6.

116. Ziacchi M, Calo L, D'Onofrio A, Manzo M, Dello Russo A, Santini L, Giubilato G, Carriere C, Santobuono VE, Savarese G, La Greca C, Arena G, Talarico A, Pisano E, Giammaria M, Pangallo A, Campari M, Valsecchi S, Diemberger I. Implantable Cardioverter Defibrillator Multisensor Monitoring during Home Confinement Caused by the COVID-19 Pandemic. Biology (Basel). 2022;11(1).

117. Zorzi A, Mattesi G, Frigo AC, Leoni L, Bertaglia E, De Lazzari M, Cipriani A, Iliceto S, Corrado D, Migliore F. Impact of coronavirus disease 19 outbreak on arrhythmic events and mortality among implantable cardioverter defibrillator patients followed up by remote monitoring: a single center study from the Veneto region of Italy. J Cardiovasc Med (Hagerstown). 2022;23(8):546-50.

118. Mascioli G, Lucca E, Napoli P, Giacopelli D. Impact of COVID-19 lockdown in patients with implantable cardioverter and cardiac resynchronization therapy defibrillators: insights from daily remote monitoring transmissions. Heart Vessels. 2021;36(11):1694-700.

119. Al Fagih A, Al Onazi M, Al Basiri S, Al-Kaf F, Dagriri K, Al Hebaishi Y, Samargandy S, Al Shengeiti L. Remotely monitored inactivity due to COVID-19 lockdowns. Potential hazard for heart failure patients. Saudi Med J. 2020;41(11):1211-6.

120. Cunha PS, Laranjo S, Lourenco A, Rodrigues L, Cardoso I, Portugal G, Valente B, Delgado AS, Ferreira RC, Abreu A, Oliveira MM. Lockdown measures for COVID-19 outbreak and variation in physical activity in patients with heart failure and cardiac implantable devices. Int J Cardiol Heart Vasc. 2021;37:100906.

121. Bartlett L, Brady JJR, Farrow M, Kim S, Bindoff A, Fair H, Vickers JC, Sinclair D. Change in modifiable dementia risk factors during COVID-19 lockdown: The

experience of over 50s in Tasmania, Australia. Alzheimers Dement (N Y). 2021;7(1):e12169.

122. Piro A, Magnocavallo M, Della Rocca DG, Neccia M, Manzi G, Mariani MV, Straito M, Bernardini A, Severino P, Iannucci G, Giunta G, Chimenti C, Natale A, Fedele F, Lavalle C. Management of cardiac implantable electronic device follow-up in COVID-19 pandemic: Lessons learned during Italian lockdown. J Cardiovasc Electrophysiol. 2020;31(11):2814-23.

123. Tsabedze N, Kinsey JH, Mpanya D, Mogashoa V, Klug E, Manga P. The prevalence of depression, stress and anxiety symptoms in patients with chronic heart failure. Int J Ment Health Syst. 2021;15(1):44.

124. Mattioli AV, Coppi F, Nasi M, Gallina S. Stress and cardiovascular risk burden after the pandemic: current status and future prospects. Expert Rev Cardiovasc Ther. 2022;20(7):507-13.

9. Bibliography of the candidate's publications

9.1. Bibliography related to the present thesis

1. **Nagy B**, Pál-Jakab Á, Kiss B, Morvai A, Sipos B, Pápai Gy, Csató G, Orbán G, Boussoussou N, Merkely B, Sótonyi P, Gerencsér A, Szilágyi B, Zima E. Influence of extreme temperatures on out-of-hospital cardiac arrest cases in Hungary: a national time-series analysis. **Resuscitation Plus.** 2026;27:101194. **(SJR: D1; IF: 3.1)**
2. **Nagy B**, Pál-Jakab Á, Orbán G, Kiss B, Fekete-Győr A, Koós G, Merkely B, Hizoh I, Kovács E, Zima E. Factors predicting mortality in the cardiac ICU during the early phase of targeted temperature management in the treatment of post-cardiac arrest syndrome - The RAPID score. Resuscitation Plus. 2024;19:100732. **(SJR: Q1; IF: 2.4)**
3. **Nagy B**, Pál-Jakab Á, Kiss B, Orbán G, Sélley TL, Dabasi-Halász Zs, Móka BB, Gellér L, Merkely B, Zima E. Remote management of patients with cardiac implantable electronic devices during the COVID-19 pandemic. Journal of Cardiovascular Development and Disease. 2023;10(5):214. **(SJR: Q1; IF: 2.4)**
4. **Nagy B**, Kiss B*, Fekete-Győr A, Pál-Jakab Á, Kovács E**, Zima E. A COVID-19-pandémia hatása a hirtelen szívmegállást követő alapszintű újraélesztésre és annak sikerességére. Orvosi Hetilap. 2023;164(13):483-487. **(SJR: Q4, IF: 0.8)**
5. **Nagy B**, Kiss B, Fülöp GÁ, Zima E. Out-of-hospital cardiac arrest in general population and sudden cardiac death in athletes. In: Zima E (ed.). Cardiac Arrhythmias - Translational Approach from Pathophysiology to Advanced Care. London: IntechOpen; 2022. https://doi.org/10.5772/intechopen.101813.

9.2. Bibliography not related to the present thesis

1. Pál-Jakab Á, Pesti P, Horti-Maricza Zs, **Nagy B**, Kiss B, Biebel B, Pápai G, Csató G, Boussoussou N, Merkely B, Gelencsér A, Sótonyi P, Szilágyi B, Zima E. Meteorological associations with out-of-hospital cardiac arrest: a national population-based time-series analysis. *Public Health*. 2026;252:106145. (IF: 3.2)
2. Kiss B, Pál-Jakab Á**, Nagy B**, Koós G, Csató G, Pápai G , Merkely B, Zima E. *Age-Treatment Interactions in Out-of-Hospital Cardiac Arrest: A Nationwide Registry Analysis.* Journal of Clinical Medicine. 2026;15(2):705. (IF: 2.9)

3. Pál-Jakab Á, Kiss B, **Nagy B**, Boldizsár I, Osztheimer I, Dévényiné ER, Kékesi V, Lóránt Zs, Merkely B, Zima E. Predicting the Higher Energy Need for Effective Defibrillation Using Machine Learning Based on an Animal Model. Journal of Clinical Medicine. 2025;14:3879. (IF: 2.9)
4. Pál-Jakab Á, **Nagy B**, Kiss B, Pápai Gy, Boussoussou N, Merkely B, Constantinovits M, Csató G, Sótonyi P, Szilágyi B, Zima E. Urban-rural disparities in out-of-hospital cardiac arrest outcomes: a nationwide Hungarian study. Resuscitation Plus. 2025;26:101108. (IF: 3.1)
5. Fekete-Győr A, Seckington A, Kiss B, **Nagy B,** Pál-Jakab Á, Kiss DZ, Fehérvári P, Zima E. The impact of the SARS-CoV-2 pandemic on in-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation Plus*. 2024;20:100756. (IF: 2.4)
6. Maár Cs, Zima E, **Nagy B**, Pál-Jakab Á, Szvath P, Kiss B, Fritúz G, Gál J, Merkely B, Kovács E.* The investigation of the efficiency of basic life support education among high school students. *Resuscitation Plus*. 2024;18:100585. (IF: 2.4)
7. Zima E, Kiss D, Pál-Jakab Á, **Nagy B**, Maár Cs, Koós G, Juhász J, Csörgő T, Juhos B, Merkely B, Pénzes M, Kiss B, Fritúz G, Kovács E. Alapszintű újraélesztés-oktatás megszervezése középiskolás diákok körében. *IME*. 2024;23(3):24-35.
8. Pál-Jakab Á, **Nagy B**, Kiss B, Zima E. The Influence of Transthoracic Impedance on Electrical Cardioversion and Defibrillation. In: Zima E (ed.). *Cardiac Arrhythmias - Translational Approach from Pathophysiology to Advanced Care*. IntechOpen; 2024. https://doi.org/10.5772/intechopen.112538
9. Kiss B, **Nagy B**, Pál-Jakab Á, Lakatos B, Soltész Á, Osztheimer I, Heltai K, Edes I, Németh E, Merkely B, Zima E. Early Application of ECMO after Sudden Cardiac Arrest. *Journal of Clinical Medicine*. 2023;12:4249. (IF: 3.0)
10. Rostás L, Tenczer J, Rostás I, Horváth-Szalai Z, **Nagy B**, Kiss B, Zima E**.** Elektromos defibrillálás, cardioversio - történeti áttekintés. *Orvosi Hetilap*. 2023 Apr 2;164(13):515-519. (IF: 0.8)

11. Szvath P, Tamáska E, **Nagy B**, Merkely B, Gál J, Zima E, Kovács E. Újraélesztés speciális körülmények között. *Orvosi Hetilap*. 2023 Apr 2;164(13):488-498. (IF: 0.8)
12. **Nagy B**, Kiss B, Pál-Jakab Á, Fülöp GÁ, Perge P, Straub É, Németh M, Kovács E, Merkely B, Zima E. Hirtelen szívhalál, újraélesztés a European Resuscitation Council 2021-es ajánlása tükrében. *Cardiologia Hungarica*. 2022;52(3):239-245.

10. Acknowledgements

First and foremost, I would like to express my sincere gratitude to Prof. Dr. Endre Zima for his continuous support, guidance, and encouragement throughout this work. His scientific mentorship, as well as the clinical training provided under his supervision, have played a central role in my professional development and greatly influenced my approach to patient care and research.

I would also like to thank Dr. Boldizsár Kiss and Dr. Ádám Pál-Jakab for their ongoing support and valuable contributions at every stage of the research process, from study design and data analysis to manuscript preparation. Their commitment and collaborative spirit were essential to the successful completion of this project.

I am grateful to all members of our research group for their collaboration, expertise, and constructive discussions, which created a supportive and stimulating scientific environment.

Furthermore, I would like to thank Prof. Dr. Béla Merkely for his continuous support of my scientific and clinical activities at the Heart and Vascular Center of Semmelweis University.

Finally, I would like to thank my family for their constant encouragement and support over the years. Their belief in me has provided a strong foundation for my academic and professional journey.