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

Ph.D. thesis

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Budapest, 2026

1. Introduction

Sudden cardiac arrest (SCA) is one of the leading causes of cardiovascular mortality worldwide and remains associated with poor survival despite major advances in resuscitation and intensive care. Out-of-hospital cardiac arrest (OHCA) represents the majority of SCA events and occurs unexpectedly outside the healthcare system, where survival rates remain low even with optimal emergency medical services and post-resuscitation care.
The clinical course of SCA can be interpreted as a multilevel process involving three interconnected stages:

1. *Population-level risk factors influencing the occurrence of cardiac arrest.*
2. *Acute and intensive care management determining early survival after return of spontaneous circulation (ROSC).*
3. *Long-term cardiovascular consequences affecting survivors after hospital discharge.*

Environmental factors, particularly extreme temperature exposure, have been increasingly recognized as potential triggers of OHCA. Acute heat or cold exposure may provoke autonomic imbalance, hemodynamic instability, and electrophysiological disorders in vulnerable individuals, thereby precipitating malignant arrhythmias and circulatory collapse.

Following successful resuscitation, the prognosis of patients is mainly determined by the complex pathophysiology of post-cardiac arrest syndrome (PCAS), which includes hypoxic-ischemic brain injury, myocardial dysfunction, and systemic inflammatory responses. Early risk stratification in the intensive care unit is therefore crucial for supporting clinical decision-making.

Finally, long-term follow-up represents an important aspect of cardiovascular care in patients at high cardiovascular risk. Heart failure progression, recurrent arrhythmias, and device-related events contribute substantially to morbidity and healthcare utilization. Cardiac implantable electronic devices and remote monitoring technologies may facilitate early detection of clinical deterioration and support individualized patient management.

While the first two studies focus on OHCA and post-resuscitation care, the third study investigates long-term outcomes in a broader population of high-risk cardiac patients with cardiac implantable electronic devices. Together, these studies address clinically relevant aspects of cardiovascular medicine, including population-level risk factors, early intensive care management, and long-term device-based follow-up.

2. Objectives

The dissertation is based on three studies investigating clinically interconnected aspects of cardiovascular medicine, including population-level vulnerability to out-of-hospital cardiac arrest, early post-resuscitation intensive care management, and long-term management of high-risk cardiac patients requiring device-based follow-up.

2.1 Temperature-related patterns of out-of-hospital cardiac arrest

The aim of this study was to investigate the association between extreme temperature exposure and the incidence of OHCA at the population level, focusing on non-linear exposure-response relationships and delayed effects.

2.2 Early prognostic assessment after ROSC: development of the RAPID score

The second objective was to identify early predictors of mortality in post-cardiac arrest patients treated with targeted temperature management (TTM) and to develop a simple prognostic score capable of estimating 30-day mortality risk within the first 12 hours after admission.

2.3 Long-term outcomes and device-based follow-up in high-risk cardiac patients

The aim of the third study was to evaluate long-term clinical outcomes, healthcare utilization, patient-reported well-being, and device-derived physiological parameters in high-risk cardiac patients with cardiac implantable electronic devices, with particular emphasis on the role of remote monitoring.

3. Methods

3.1. Temperature-related patterns of out-of-hospital cardiac arrest

A nationwide population-based time-series analysis was conducted by linking the OHCA case database of the Hungarian National Ambulance Service (HNAS) with meteorological data provided by Hungarian Meteorological Service (HungaroMet). The study period covered 1,887 consecutive days between November 2018 and December 2023 (Reference Numbers: IV/3043/2021/EKU and IV/3043-3/2021/EKU).

Extreme temperature exposures were defined using percentile-based thresholds derived from the Hungarian temperature distribution. Heatwaves were defined as ≥3 consecutive days with daily mean temperature ≥27.1 °C (95th percentile of the warm-season distribution), while cold spells were defined as ≥2 consecutive days with minimum temperature ≤−9.2 °C (2nd percentile of the cold-season distribution).

The association between temperature exposure and daily OHCA counts was analyzed using negative binomial regression models to account for overdispersion in daily event counts. Models were adjusted for day of the week, calendar month, and year to control for temporal confounding.

To evaluate delayed temperature effects, distributed lag non-linear models (DLNM) were applied using a 21-day lag structure, allowing characterization of both non-linear exposure-response relationships and delayed risk patterns associated with heat and cold exposures.

Sensitivity analyses were performed using alternative definitions of heatwaves and cold spells, and sex-stratified models were used to evaluate potential effect modification.

3.2. Early prognostic assessment after return of spontaneous circulation (ROSC): development of the RAPID score

The second study was a single-center retrospective cohort analysis conducted at the Heart and Vascular Center of Semmelweis University between January 2016 and December 2022. Adult patients (≥18 years) with OHCA who remained comatose after ROSC and were admitted to the cardiac intensive care unit were eligible for inclusion (approval number: 194/2020). All included patients underwent targeted temperature management (TTM) according to the institutional protocol, with a target temperature of 33 °C.

Clinical, laboratory, and echocardiographic parameters obtained during the early intensive care phase after admission were systematically collected from electronic medical records and intensive care documentation. Variables describing the circumstances of cardiac arrest, demographic characteristics, admission laboratory values, arterial blood gas parameters, and early echocardiographic findings were included in the analysis.
The primary outcome of the study was 30-day mortality.

To identify predictors of outcome, associations between candidate variables and mortality were examined using regression-based modeling approaches. Variables demonstrating independent prognostic value were incorporated into a multivariable model.

Model discrimination was evaluated using receiver operating characteristic analysis, while calibration and robustness were assessed through bootstrap-based internal validation with 10,000 resamples.

3.3. Long-term outcomes and device-based follow-up in high-risk cardiac patients

The third study evaluated the impact of remote monitoring on clinical outcomes and healthcare utilization in high-risk cardiac patients with cardiac implantable electronic devices (CIEDs) followed at our tertiary referral center. This retrospective single-center analysis included adult patients equipped with CIEDs capable of remote monitoring transmission, allowing continuous collection of device based and derived diagnostic data (approval number: 106/2020).

The study was conducted during the COVID-19 pandemic period in 2020, when major changes occurred in healthcare delivery. Three predefined periods were analyzed according to the organization of medical care: the pre-pandemic period, the lockdown period associated with pandemic-related restrictions, and the post-lockdown period following the lifting of restrictions.

Several outcome domains were evaluated. First, clinical events related to heart failure progression were assessed, including episodes of acute decompensation requiring hospital admission. Second, changes in healthcare utilization were analyzed by comparing the number of outpatient visits between the year preceding the pandemic and the first pandemic year.

In addition, patient-reported outcomes reflecting symptoms and quality of life were assessed using validated questionnaires administered during telephone consultations. Heart failure-specific health status was evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ), while general health-related quality of life was assessed using the EQ-5D-5L instrument.

Finally, objective parameters derived from remote monitoring systems were evaluated, including heart rate characteristics, heart rate variability, arrhythmia episodes, pacing parameters, and device-recorded patient activity levels.

4. Results

4.1. Temperature-related patterns of out-of-hospital cardiac arrest

Traumatic arrests, intoxication-related events, drowning, obstetric causes, and cases without reliable geographic linkage to meteorological data were excluded. The final analytical dataset included 116,579 OHCA cases in which cardiopulmonary resuscitation was initiated by HNAS. The mean age of patients was 67 years, and the majority of events occurred at home (73%). Further details are provided in Table 1.

Table 1. Baseline epidemiological characteristics of the Hungarian OHCA cohort. 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
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)

Characteristic	Value
Other locations, n (%)	10,500 (9.0)

A marked seasonal variation was observed, with higher OHCA incidence during the colder months compared with the warm season.

Distributed lag non-linear model analysis demonstrated a non-linear association between ambient temperature and OHCA incidence. The cumulative exposure-response curve showed a U-shaped relationship, with the lowest estimated risk observed at approximately 19 °C, corresponding to the minimum mortality temperature (Figure 1).

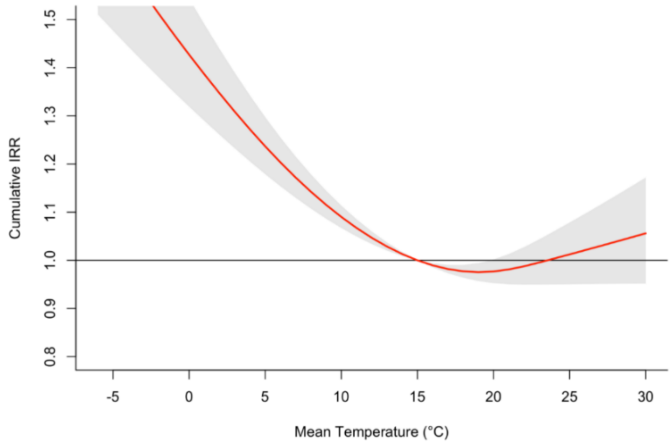

Figure 1. Overall Cumulative Exposure-Response (source: Nagy B, et al. Resuscitation Plus. 2026;27:101194. CC BY 4.0).

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MMT, minimum mortality temperature; OHCA, out-of-hospital cardiac arrest.

Exposure to extreme heat was associated with a rapid increase in OHCA risk, with the strongest effect observed on the day of exposure (lag 0) and within the first 1-2 days.

In contrast, cold exposure demonstrated a delayed and more prolonged association, with the risk beginning to increase approximately 2-3 days later and persisting for up to around 10 days following the temperature decrease.

The DLNM confirmed distinct temporal dynamics, demonstrating acute heat-related effects and delayed cumulative cold-related risk. The lag-response relationship between extreme temperature exposure and OHCA incidence is illustrated in Figure 2.

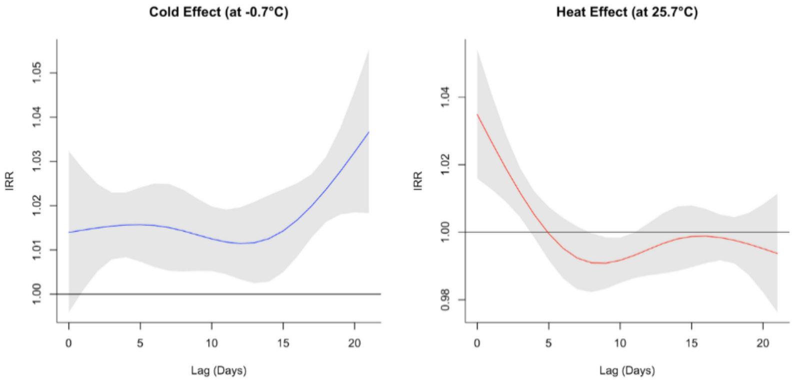

Figure 2. Lag-Specific Effects of Cold and Heat Exposure on OHCA Incidence (source: Nagy B, et al. Resuscitation Plus. 2026;27:101194. CC BY 4.0).
Abbreviations: CI, confidence interval; DLNM, distributed lag non-linear model; IRR, incidence rate ratio; OHCA, out-of-hospital cardiac arrest

Sensitivity analyses using alternative exposure definitions yielded consistent results, confirming the robustness of the findings, while sex-stratified analyses showed comparable temperature-OHCA patterns in men and women.

4.2. Early prognostic assessment after ROSC: development of the RAPID score

In the second study, we evaluated early predictors of mortality in patients with OHCA treated with TTM at our clinic. A total of 135 patients were included in the analysis, with a mean age of 64 years.

More than one hundred early clinical and laboratory parameters obtained during the first hours of intensive care were evaluated in relation to short-term mortality. In multivariable analysis, five variables remained independently associated with 30-day mortality: heart rate ($p = 0.001$), initial rhythm ($p = 0.009$), age ($p = 0.012$), arterial pH ($p = 0.017$), and right ventricular end-diastolic diameter ($p = 0.034$)

These parameters were integrated into a simple prognostic model, the RAPID score, which allows estimation of mortality risk using variables that are routinely available shortly after admission. The model demonstrated good discriminative performance, with an apparent AUC of 0.84 for predicting 30-day mortality. After internal validation using 10,000 bootstrap resamples, the optimism-corrected AUC remained high at 0.82, confirming the robustness of the model and its stable predictive performance.

To facilitate clinical ease of use, the model was also implemented as an online calculator, which allows rapid bedside estimation of individual mortality risk: https://rapid-score.streamlit.app.

The RAPID nomogram and the estimated probability of 30-day mortality are presented in Figure 4.

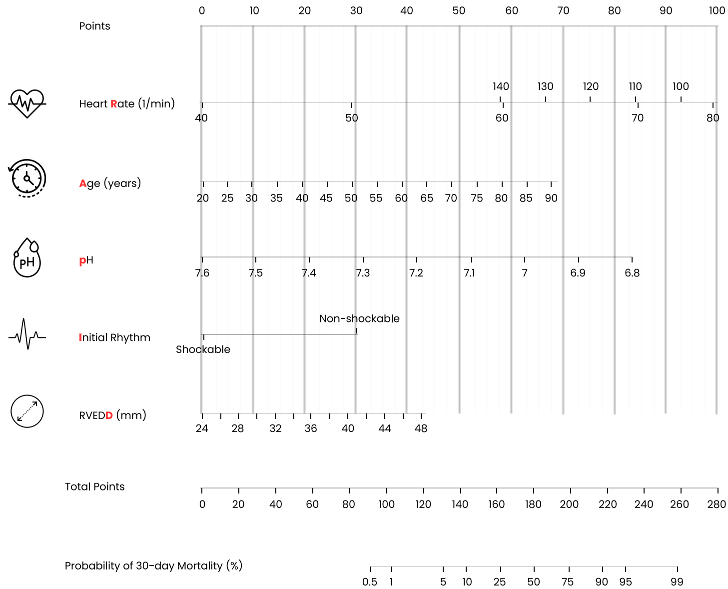

Figure 4. The RAPID score nomogram is a tool used to estimate the mortality risk for out-of-hospital cardiac arrest patients undergoing TTM (source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0). Abbreviations: RVEDD, right ventricular end-diastolic diameter; TTM, targeted temperature management.

4.3. Long-term outcomes and device-based follow-up in high-risk cardiac patients

In the third study, 85 patients with heart failure and cardiac implantable electronic devices were included. Device distribution consisted of 41 CRT-P (48.2%), 23 CRT-D (27.1%), and 21 conventional ICD (24.7%) implantations.

During the lockdown period, the number of in-office outpatient visits decreased by 42.5% compared with the corresponding period of the previous year. After the lifting of restrictions, a compensatory increase in visits was observed; however, when comparing the full year before and after the outbreak of the pandemic, 159 in-person follow-up visits were recorded before the lockdown and 116 visits in the year following (p=0.008).

Despite the reduction in in-person follow-up, the incidence of acute heart failure decompensation events did not increase, with 5 events in the year preceding the lockdown and 7 events in the year following the outbreak (p = 0.60).

Overall, heart failure-related symptoms remained stable; however, two parameters related to psychological well-being showed significant changes during the lockdown period, namely the EQ-5D-5L anxiety/depression dimension and the self-rated overall health status.

Objective parameters obtained from remote device monitoring remained largely stable (Table 2).

Table 2. The results of remote monitoring parameters (source: Nagy B, et al Resuscitation Plus. 2024;19:100732. CC BY 4.0).

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

Parameter	Pre-pandemic (mean ± SD)	Lockdown (mean ± SD)	After lockdown (mean ± SD)	p-value
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 increased significantly across the study periods ($p = 0.013$), with post-hoc analysis confirming a difference between the pre- and post-lockdown periods ($p = 0.03$). Age-stratified analysis showed that this increase was driven by patients younger than 70 years, while no significant change was observed among patients aged ≥70 years.

5. Conclusions

The present dissertation examined three clinically interconnected aspects of cardiovascular medicine, including population-level determinants of OHCA, early prognostic assessment following successful resuscitation, and long-term management of high-risk cardiac patients requiring device-based follow-up.

At the population level, OHCA cases demonstrated a non-linear U-shaped association between ambient temperature and OHCA incidence. Both heat and cold exposures were associated with increased risk; however, the temporal patterns differed markedly. Heat exposure produced an early and transient increase in OHCA risk, whereas cold exposure resulted in a delayed and more sustained elevation of risk over several subsequent days. These findings support the concept that extreme temperatures act primarily as acute triggers in vulnerable populations, likely through hemodynamic stress, autonomic imbalance, and increased arrhythmic risk. The observed delayed effect of cold exposure is consistent with previous epidemiological observations suggesting that prolonged physiological stress, including vasoconstriction, and increased blood pressure may gradually increase cardiovascular instability.

The second component of the dissertation focused on early prognostic assessment in patients admitted to intensive care after OHCA. In this cohort, early mortality risk during targeted temperature management could be estimated using routinely available clinical parameters obtained within the first hours of ICU admission. The RAPID score, incorporating heart rate, age, arterial pH, initial cardiac rhythm, and right ventricular end-diastolic diameter, demonstrated good predictive performance for 30-day mortality. Importantly, these parameters are easily accessible in routine clinical practice, allowing early bedside risk stratification without the need for complex or delayed diagnostic tests. Early identification of high-risk patients may support more individualized monitoring strategies and may assist clinicians in anticipating potential hemodynamic or organ dysfunction during the early post-resuscitation phase.

Finally, the third component of the dissertation examined long-term follow-up in a broader population of high-risk cardiac patients with cardiac implantable electronic devices. In this cohort, key indicators of heart failure status, arrhythmia burden, and device-derived physiological parameters remained largely stable despite substantial reductions in conventional outpatient follow-up during the COVID-19 pandemic. These findings underline the growing importance of device-based telemonitoring in the management of selected vulnerable cardiovascular populations.

Taken together, the findings of this dissertation provide insight into complementary aspects of cardiovascular care, ranging from population-level vulnerability and environmental risk factors to intensive care prognostication and long-term device-based follow-up. Improved understanding of these factors may contribute to better risk stratification, more individualized patient management, and optimized cardiovascular care across different clinical settings.

6. Bibliography of the candidate's publications

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