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Investigation of Pathophysiology, Interventions, Prognostic and Mortality Factors in Conditions Requiring Cardiopulmonary Resuscitation

Ph.D. thesis

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List of Abbreviations

ABG – Arterial Blood Gas

AED – Automated External Defibrillator

AQI – Air Quality Index

AUC – Area Under the Curve

BE – Base Excess

CA – Cardiac Arrest

CI – Confidence Interval

COVID-19 – Coronavirus Disease 2019

CPR – Cardiopulmonary Resuscitation

DFT – Defibrillation Threshold

DTR – Diurnal Temperature Range

EMS – Emergency Medical Services

F_1 score – Harmonic Mean of Precision and Recall

FN – False Negative

FP – False Positive

GDPR – General Data Protection Regulation

HCO_3^- – Bicarbonate

Hct – Hematocrit

HNAS – Hungarian National Ambulance Service

ICU – Intensive Care Unit

IQR – Interquartile Range

IRR – Incidence Rate Ratio

K^+ – Potassium

KDE – Kernel Density Estimation

ML – Machine Learning

Na^+ – Sodium

OHCA – Out-of-Hospital Cardiac Arrest

OR – Odds Ratio

$PaCO_2$ – Partial Arterial Pressure of Carbon Dioxide

PaO_2 – Partial Arterial Pressure of Oxygen

PEA – Pulseless Electrical Activity

PSM – Propensity Score Matching

R^2 – Coefficient of Determination

RH – Relative Humidity

RMSE – Root Mean Squared Error

ROSC – Return of Spontaneous Circulation

SD – Standard Deviation

SHAP – SHapley Additive exPlanations

SMD – Standardized Mean Difference

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

TN – True Negative

TP – True Positive

VF – Ventricular Fibrillation

VT – Ventricular Tachycardia

VIF – Variance Inflation Factor

WEI – Weather Index

XGBoost – eXtreme Gradient Boosting

1. Introduction

Out-of-Hospital Cardiac Arrest: Multi-Level Factors Affecting Outcomes

1.1 Out-of-Hospital Cardiac Arrest: A Global Public Health Challenge

Out-of-hospital cardiac arrest (OHCA) is one of the most time-critical emergencies in medicine, characterized by sudden cessation of cardiac mechanical activity with circulatory collapse, unconsciousness, and respiratory arrest [1]. Despite decades of advances in resuscitation science and emergency medical systems, OHCA continues to impose a substantial global burden, with survival outcomes that remain low even in high-resource settings [2].

1.1.1 Epidemiology and Burden

Global OHCA incidence varies geographically, reflecting differences in demographics, risk-factor prevalence, EMS capabilities, and case ascertainment [3]; across European populations it ranges from 67 to 170 per 100,000 annually [3, 4]. Ventricular fibrillation (VF) and ventricular tachycardia (VT) together account for approximately 20% of cases – the shockable rhythms requiring immediate defibrillation – while the remaining 80% present with non-shockable asystole or pulseless electrical activity (PEA), which carry substantially lower survival and do not respond to defibrillation [1, 5].

Mortality remains persistently high regardless of resource availability [6]: survival to hospital discharge stays below 10% in most populations, and 5% or lower in many [7]. Among survivors, neurological sequelae frequently impair quality of life [8, 9].

International registry data show pronounced seasonal variation, with substantially higher winter OHCA incidence across diverse regions [10] – a consistent pattern implicating environmental and behavioural determinants that warrant systematic investigation (Figure 1).

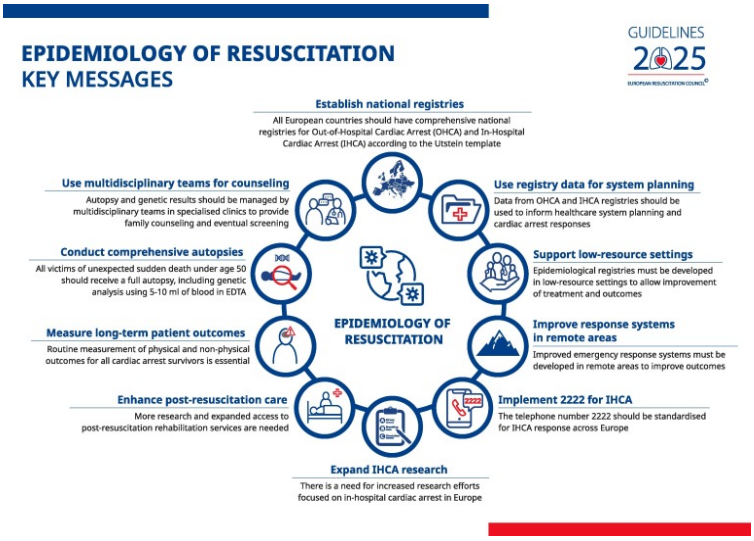

Figure 1. Key Messages on Epidemiology in Resuscitation from the 2025 Guidelines of the European Resuscitation Council [11]

Beyond clinical outcomes, OHCA imposes a substantial economic burden through EMS deployment, ICU resources, prolonged stays, post-resuscitation care, and rehabilitation [12-14]. Its high mortality and morbidity, combined with rising incidence in aging populations, make OHCA a public-health priority warranting investigation across individual, environmental, and system levels [15].

1.1.2 Physiological Determinants of Resuscitation Success

Successful cardiac arrest (CA) management requires understanding the pathophysiology determining arrest occurrence and resuscitation probability. CA arises from diverse processes converging on loss of effective cardiac mechanical activity, with VF the most common shockable rhythm [1]. The Chain of Survival emphasizes rapid, sequential interventions, with prompt defibrillation the definitive treatment for shockable rhythms [16, 17].

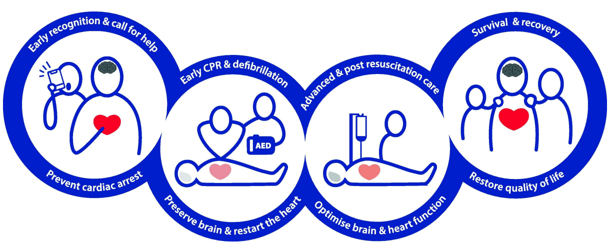

Figure 2. The Chain of Survival Based on the 2025 Guidelines of the European Resuscitation Council [11]

Resuscitation effectiveness depends critically on myocardial physiological state: acid-base balance, electrolyte disturbances (particularly sodium and potassium), oxygenation, and haematological factors influence myocardial electrical properties and defibrillation responsiveness [18]. In monitored settings with established arterial access (catheterization laboratories, cardiac surgery operating rooms, ICUs), arterial blood gas (ABG) parameters provide real-time physiological information, whereas such data are rarely available prehospital. Physiological parameter-guided decision-making is therefore relevant mainly to in-hospital settings and complements, rather than replaces, guideline-based defibrillation; its utility for anticipating intervention needs remains underexplored.

1.2 Defibrillation as Definitive Treatment

Electrical defibrillation is the definitive therapy for VF and VT and a time-dependent step in the Chain of Survival [11, 16, 17]. It terminates disorganized myocardial activation by delivering a brief high-energy pulse that simultaneously depolarizes a critical mass of cardiomyocytes, allowing an organized rhythm to re-emerge. Effectiveness is strongly time-sensitive, as ongoing fibrillation rapidly worsens metabolic derangement and electrical instability, reducing the probability that later shocks succeed [19, 20].

Contemporary practice follows standardized energy protocols to minimize delays and simplify decisions under stress. Although essential prehospital, these protocols do not account for inter-individual variability in shock responsiveness. Energy selection involves a trade-off: higher settings may improve success in some patients but can prolong capacitor charge time, delaying shock delivery, and expose the myocardium to greater electrical injury and post-shock dysfunction [21-24]. This supports identifying cases likely to require higher energy, rather than defaulting to maximal energy for all shocks.

The defibrillation threshold (DFT), the minimum energy reliably terminating VF, illustrates why standardized protocols cannot fit all cases. DFT is not fixed: it reflects a dynamic interplay between technical factors (waveform, electrode position, transthoracic impedance) and biological factors modulating myocardial excitability and current distribution. Acute physiological conditions, including acid-base disturbances, oxygenation, electrolyte shifts, and hematocrit, can alter membrane potentials, conduction, and refractoriness, plausibly shifting energy requirements [18, 25].

This thesis adopts the premise that, in monitored settings where arterial access and serial blood gas assessment are already routine, readily obtainable physiological information may help anticipate elevated energy requirements and guide individualized defibrillation. This is intended not to replace guideline-based prehospital defibrillation, but to support personalized decisions where refractory ventricular arrhythmias and repeated shocks are managed and additional physiological data are immediately available.

1.3 Machine Learning in Cardiac Arrest Research

OHCA research poses analytical challenges beyond linear modeling. Defibrillation energy requirements vary with complex interactions among physiological parameters, and meteorological influences involve nonlinearities, temporal lags, and threshold effects across multiple variables. Classical models remain indispensable for transparent effect estimation and hypothesis testing; however, when the objective is prediction from complex multivariable data, machine learning offers complementary capabilities.

Interpretable machine-learning methods complement this toolkit: tree-based ensembles capture nonlinear decision boundaries and predictor interactions while remaining interrogable through established interpretability techniques. In medical applications, rigorous internal validation and calibration are essential, because overly flexible models can overfit training data and yield misleadingly optimistic performance.

Within this thesis, machine learning is positioned as a pragmatic extension of classical methods, used where the question concerns prediction under complex multivariable structure rather than average effects, notably micro-level prediction of elevated defibrillation energy from physiological parameters and macro-level forecasting of daily OHCA incidence from multiple meteorological variables.

1.4 Environmental Determinants of Cardiovascular Events

Relationships between environmental conditions and cardiovascular events have been investigated for decades, revealing complex associations between meteorological parameters and cardiac emergencies. Understanding these determinants enables predictive systems, targeted public-health interventions, and improved resource allocation during high-risk periods, increasingly relevant as climate change alters weather patterns and extremes.

Cardiovascular risk shows clear seasonal and meteorological variation, with OHCA incidence generally higher in winter and ambient temperature the most consistently associated factor. Cold exposure raises sympathetic tone, blood pressure, and viscosity and may promote plaque instability, whereas heat imposes thermoregulatory stress and fluid shifts. Other parameters (pressure, wind speed, humidity, air quality) show context-dependent associations, and effects can occur with short lags over subsequent days.

Most prior meteorological-OHCA studies analyzed single cities or limited regions [26-28], used heterogeneous methods that hinder comparison, and examined narrow parameter sets, often temperature alone. Lag-structure investigation has been incomplete, with incomparable specifications, and extreme-weather analyses remain sparse despite their policy relevance. National-level analyses with systematic multi-parameter lag investigation are particularly scarce for Continental-climate, Central-Eastern European settings.

Climate models project more frequent extreme heat, cold snaps, and weather variability, with substantial implications for cardiac-emergency burden. Early-warning systems integrating meteorological forecasts with population health surveillance could enable proactive interventions during predicted high-risk periods, making weather-responsive healthcare planning increasingly important for EMS preparedness.

1.5 Healthcare System Factors and Geographic Disparities

While physiological and environmental factors shape OHCA incidence, healthcare-system organization and geographic resource distribution critically determine outcomes once arrest occurs. System-level factors act through EMS response capability, resource distribution, protocol standardization, and care coordination, producing geographic survival disparities that reflect both inherent challenges and modifiable system characteristics.

1.5.1 Emergency Medical Services and Urban-Rural Context

Urban areas benefit from shorter distances to patients, higher EMS unit density enabling faster dispatch, better roads, and closer proximity to advanced cardiac care. Rural areas face longer travel distances, lower population density, fewer EMS units per capita, more challenging terrain, and greater distances to definitive care.

Rural health disadvantage is documented across multiple dimensions beyond emergency care: geographic distance to facilities, provider shortages, limited advanced diagnostics and subspecialty access, and care-coordination challenges [29, 30]. These affect diverse outcomes, including cardiovascular mortality, cancer survival, maternal mortality, and chronic-disease management [31-33]. For time-critical emergencies such as OHCA, where minutes determine survival, geographic factors may exert particularly pronounced effects.

1.5.2 Urban-Rural OHCA Disparities: Evidence and Mechanisms

Studies from North America, Europe, Australia, and Asia consistently document urban-rural disparities in OHCA survival, with rural settings showing lower survival even after adjustment for demographics and arrest characteristics [4, 7, 34]. This consistency across diverse healthcare systems suggests fundamental mechanisms related to time-critical intervention access rather than system-specific factors.

Longer rural EMS response times are the most obvious mechanism: international studies show rural areas meeting guideline-recommended response targets far less often [35]. Given the time-dependence of resuscitation, with survival falling rapidly per minute of defibrillation delay in shockable rhythms, these differences alone could substantially drive the observed survival disparities.

Additional mechanisms may contribute. Lower rural bystander-CPR rates may reflect lower population density (fewer witnessed arrests), variable community preparedness, or differing CPR-training rates. Distance to definitive care affects not only initial response but also transport to hospitals offering advanced post-arrest care, including imaging, interventional cardiology, targeted temperature management, and specialized ICUs.

1.5.3 Methodological Challenges and Central-Eastern European Context

Urban and rural populations differ systematically in age, risk factors, and behaviours, so rigorous confounding control is required to isolate geography-related effects [36-39].

Hungary's centralized national EMS offers a clean context, minimizing organizational heterogeneity while preserving geographic variation.

1.6 The Hungarian National Ambulance Service Registry

The Hungarian National Ambulance Service (HNAS) is a unified, centralized national EMS covering Hungary's entire population [40]. Single-provider nationwide coverage ensures every EMS-attended OHCA is recorded, providing population-based data without geographic gaps, with uniform protocols and identical personnel training. The registry links to comprehensive meteorological data and maintains consistent urban-rural classification based on official administrative categories.

1.7 Knowledge Gaps and Study Rationale

A comprehensive literature review across three domains (individual physiological determinants of defibrillation success, environmental/meteorological determinants of OHCA incidence, and healthcare system determinants of urban-rural outcome disparities) reveals substantial evidence bases but also critical knowledge gaps warranting systematic investigation.

1.7.1 Summary of Current Knowledge

Defibrillation is the definitive treatment for VF and VT, and time to defibrillation strongly predicts survival [17, 35, 41]; nevertheless, clinical energy selection remains standardized and largely non-personalized [11, 42]. Implantable cardioverter-defibrillator testing has identified clinical predictors of elevated thresholds, including specific medications, structural heart disease, and left ventricular dysfunction [43, 44], but in contexts fundamentally different from emergency external defibrillation, and acute physiological parameters have rarely been examined as predictors despite their clear biological plausibility.

Meteorological influences on cardiovascular events are well documented, with consistent winter increases in OHCA incidence across diverse regions, climates, and populations [10, 45], operating through autonomic, haemodynamic, rheological, and inflammatory mechanisms [46-48]. However, most studies analysed single cities with heterogeneous lag specifications, and extreme weather events remain little studied (see Section 1.4). Urban-rural outcome disparities are similarly consistent internationally, with rural settings showing worse survival even in high-resource systems [4, 7, 34]; longer rural response times explain only part of this gap, propensity-based analytical methods have been underutilized, and Central-Eastern European evidence is limited.

1.7.2 Specific Knowledge Gaps

Gap 1: Can readily available physiological parameters predict optimal defibrillation energy requirements?

Despite well-established effects of acid-base status, electrolytes, oxygenation, and hematocrit on myocardial electrical properties and defibrillation success in experimental models [18, 25], no validated model exists for individualized external defibrillation energy selection. This represents a missed opportunity, because arterial blood gas (ABG) measurements are already obtained routinely in the monitored settings where refractory ventricular arrhythmias are managed – cardiac catheterization laboratories, cardiac surgery operating rooms, and ICUs – whereas prior DFT studies addressed implantable-device patients under fundamentally different conditions [43, 44]. Whether ABG parameters predict defibrillation energy requirements, and whether machine learning can exploit such relationships for individualized energy selection, remains unresolved.

Gap 2: What is the comprehensive country-level relationship between meteorological factors and OHCA incidence?

Although temperature is an established meteorological risk factor for OHCA, most studies analysed single cities or limited regions, examined restricted parameter sets, used incomparable lag specifications, and characterized extreme weather events incompletely [26]. National-level analyses combining comprehensive meteorological data, systematic multi-parameter lag-structure investigation, and rigorous extreme-event characterization remain sparse, and are particularly lacking for Continental-climate, Central-Eastern European settings. The comprehensive country-level relationship between multiple meteorological parameters and daily OHCA incidence – including delayed (multi-day) effects and machine-learning-detectable nonlinearities – therefore remains unresolved.

Gap 3: What is the magnitude and mechanism of urban-rural OHCA survival disparities in Hungary?

International evidence consistently demonstrates urban-rural survival disparities, yet Hungarian data are lacking, and it remains uncertain whether disparities in a centralized, post-transition Central-Eastern European system match the magnitude and pattern reported elsewhere. Methodologically, urban and rural populations differ systematically on outcome-relevant characteristics, so standard regression may inadequately control for confounding, whereas propensity score matching – underutilized in this literature – permits less biased estimation of the geographic effect. The magnitude of any disparity in Hungary after rigorous matching, how it varies continuously across the response-time spectrum, and whether it concentrates in specific clinical subgroups remain to be established.

1.7.3 Unified Rationale

The three studies are complementary, examining OHCA from individual/physiological (micro), environmental/temporal (macro), and system/geographic (meso) perspectives to build a multi-level understanding of the modifiable determinants of survival. At the micro-level, individual physiology may modulate the effectiveness of interventions, enabling personalized approaches in monitored settings; at the macro-level, population-level risk fluctuates predictably with environmental conditions, enabling anticipatory resource allocation during forecast high-risk periods; at the meso-level, healthcare-system organization and geographic resource distribution determine whether time-critical interventions reach patients quickly enough to affect survival. This framework reflects the recognition that complex health outcomes require the simultaneous investigation of individual-, environmental-, and system-level factors rather than any single level in isolation.

2. Objectives

2.1 General Aims

OHCA remains a critical public health challenge with survival rates consistently around or below 10% across Europe. OHCA pathophysiology, interventions, and outcomes are influenced by a complex interplay of factors operating at multiple analytical levels – from individual physiological parameters through geographic disparities to environmental determinants. This dissertation aimed to investigate these multi-level determinants through three complementary studies spanning micro-level (individual physiological factors affecting defibrillation), meso-level (geographic disparities in emergency response), and macro-level (environmental influences on incidence) analyses. These investigations were designed to provide actionable evidence for improving OHCA outcomes through personalized interventions, system optimization, and preventive strategies.

2.2 Specific Objectives

This dissertation pursued three interconnected research objectives, each addressing a distinct analytical level of OHCA investigation:

Objective 1: MICRO-Level Analysis – Predicting Defibrillation Energy Requirements Using Physiological Parameters

Early defibrillation improves outcomes in cardiac arrests with shockable rhythms, but optimal defibrillation energy requirements remain debated. The first objective was to investigate whether ABG parameters were associated with defibrillation energy requirement and whether they could discriminate between lower and higher DFT categories in controlled clinical environments. Specifically, this study aimed to:

- Determine associations between ABG parameters and DFT values in a standardized experimental protocol.
- Classify cases requiring higher versus lower initial defibrillation energy based on physiological parameters.
- Identify the most important physiological predictors of defibrillation energy requirements.

- Provide proof-of-concept evidence supporting the potential feasibility of more individualized defibrillation strategies in controlled clinical settings where ABG measurements are readily available

Objective 2: MACRO-Level Analysis – Quantifying Meteorological Associations with OHCA Incidence

Meteorological factors may influence the incidence of cardiovascular emergencies, but comprehensive national evidence on the associations between OHCA and meteorological factors remains limited. The second objective was to comprehensively investigate meteorological associations with OHCA occurrence using complete national population data. Specifically, this study aimed to:

- Quantify associations between atmospheric conditions, extreme weather events and daily OHCA incidence across multiple meteorological parameters.
- Characterize temporal lag patterns in weather-OHCA relationships.
- Provide evidence for developing weather-based early warning systems and targeted prevention strategies.

Objective 3: MESO-Level Analysis – Investigating Urban-Rural Disparities in OHCA Outcomes

OHCA outcomes often differ between urban and rural settings, but comprehensive nationwide analyses using rigorous confounding control methods such as propensity score matching remain limited. The third objective was to investigate urban-rural disparities in OHCA outcomes through an extensive nationwide analysis of all OHCA cases in Hungary. Specifically, this study aimed to:

- Identify key factors contributing to on-scene survival rates in urban and rural settings.
- Quantify the independent effect of geographic location after adjusting for patient demographics, arrest characteristics, and emergency medical service response variables.
- Characterize how urban-rural survival differences vary across the emergency response-time spectrum.
- Identify targets for system-level interventions to strengthen the Chain of Survival in rural communities.

3. Methods

3.1 Overview of Research Protocols

All three studies used statistical and machine-learning methods matched to their questions: Study 1, a controlled animal-model experiment relating ABG parameters to DFT; Study 2, a population-based time-series analysis of national registry data quantifying meteorological associations with OHCA; and Study 3, a nationwide registry analysis using propensity score matching and multivariable regression to assess urban-rural survival disparities.
For Studies 2 and 3, the centralized digital HNAS registry provided a unified national data infrastructure capturing all EMS-attended OHCA cases, with standardized collection, uniform training, and consistent clinical practice across regions.

3.1.1 Ethical Approvals and Regulatory Compliance

The animal study (Study 1) was approved by the Ethics Committee of Hungary for Animal Experimentation (approval number 22.1/1163/3/2010, 22 June 2010) and conformed to European Directive 2010/63/EU [49] and the Guide for the Care and Use of Laboratory Animals [50]. The registry-based studies (Studies 2 and 3) were approved by the Hungarian Medical Research Council (IV/3043/2021/EKU and IV/3043-3/2021/EKU), complied with GDPR, and adhered to the Declaration of Helsinki [51], individual consent was waived for retrospective analysis of anonymized national data.

3.2 Study 1: Defibrillation Threshold Prediction Using Machine Learning

3.2.1 Experimental Design and Animal Model

A protocol-based stepwise defibrillation approach in a canine model related ABG parameters to DFTs, enabling precise determination of the minimum energy for successful defibrillation and its correlation with physiological parameters measured immediately before each attempt, under a standardized, strictly controlled protocol.
The experimental phase was conducted at Semmelweis University (Budapest, Hungary) in accordance with Good Laboratory Practice regulations. Fifteen healthy male Beagle dogs (10-11 kg) with normal baseline ABG parameters and no underlying pathologies

were used. Animals were anesthetized with pentobarbital (30 mg/kg intravenously), administered with tramadol (2 mg/kg intravenously) for analgesia, intubated, and mechanically ventilated. This standardized anesthetic protocol was applied identically to every animal; because pentobarbital is recognized to modestly elevate the defibrillation threshold, its effect was systematic and non-differential across all determinations and energy categories. Continuous monitoring was established via invasive blood pressure measurement and electrocardiography.
Pediatric defibrillation pads (8 cm diameter, Innomed Medical Inc., Budapest, Hungary) were placed lateral-lateral on the shaved chest to standardize delivery and minimize transthoracic-impedance variability [42]. A modified prototype defibrillator (legacy Innomed Cardio-Aid 360-B motherboard) connected to a PC recorded continuous electrophysiological data, with an Innomed Cardio-Aid 360-B backup unit; all procedures followed a uniform methodology and timeline.

3.2.2 Defibrillation Protocol and DFT Determination

The DFT is the minimum energy reliably terminating VF, thresholds were confirmed retrospectively after failure at a lower energy. ABG-DFT correlations informed predictive model development to identify cases requiring higher initial energy.
Biphasic truncated-waveform shocks were used for all defibrillation attempts. Transthoracic impedance was continuously monitored, and energy was automatically adjusted to compensate for changes in impedance from successive shocks, ensuring consistent energy delivery across attempts. Ventricular fibrillation was induced using 50 Hz alternating current for 3 seconds. After a 10-second VF period, the defibrillation protocol was initiated.
DFT was determined by stepwise energy titration (Figure 3). After baseline ECG, invasive blood pressure, and blood sampling, VF was induced (50 Hz alternating current, 3 s) and, after a 10-second VF period, a shock was delivered. Starting at 100 J, energy was decreased by 10 J after each success until failure defined the DFT as the lowest successful level; a 150 J rescue shock followed failure, with 3-minute stabilization between attempts. Failed initial 100 J attempts triggered 10 J step-ups until success.

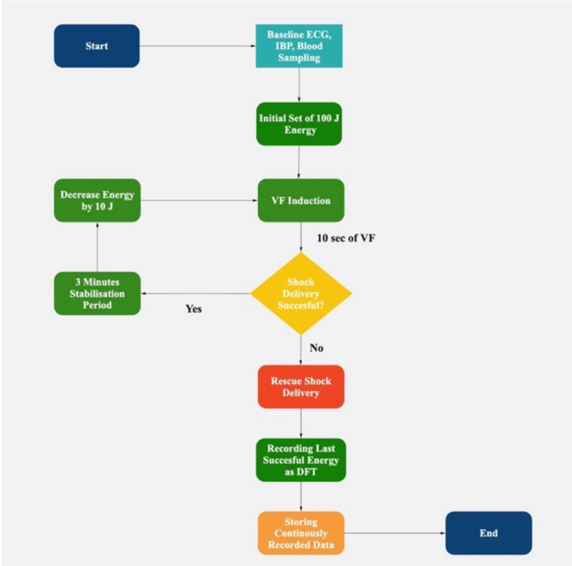

Figure 3. Stepwise defibrillation protocol for DFT determination.

3.2.3 Data Collection and Statistical Analysis

ABG samples were collected immediately before each ventricular fibrillation induction. Parameters measured included partial arterial pressure of carbon dioxide ($PaCO_2$), partial arterial pressure of oxygen (PaO_2), pH, hematocrit, sodium (Na^+), potassium (K^+), and bicarbonate (HCO_3^-) levels. During the experimental phase of the research, defibrillations were performed on 15 experimental animals, resulting in 2,100 shock deliveries. Based on this data, 113 DFT values were determined using the energy-selective stepwise defibrillation protocol.

Relationships among laboratory parameters were examined using correlation heatmaps and scatter plots to identify patterns and assess multicollinearity [52, 53]. Normality was assessed with the Shapiro-Wilk test, predefined two-group comparisons between lower and higher DFT categories used the Wilcoxon rank-sum test (significance $p < 0.05$), and Spearman correlation evaluated ABG-DFT associations. Analyses used Python 3.8 with Visual Studio Code (1.99.0-insider) [54, 55]. To confirm that acid-base status remained stable across repeated inductions, first-versus-last pre-induction ABG values were compared within each animal using a paired test (paired t-test or Wilcoxon signed-rank test, as appropriate), revealing no statistically significant drift.

3.2.4 Machine Learning Model Development and Validation

Multicollinearity was assessed using variance inflation factor values, with values exceeding 5 indicating significant collinearity. Variables with high variance inflation factor values (pH, Na^+, K^+) were evaluated individually, and features with high correlation and high variance inflation factor were compared pairwise, retaining only one to enhance model stability.

Model development used supervised classification to identify higher-DFT cases from ABG parameters. Continuous DFTs were dichotomized into lower versus higher energy requirement (40 J and 130 J). These thresholds were grounded in both the data and the protocol: 40 J corresponded to the cohort median DFT (the most frequent lower-energy requirement), whereas 130 J represented the upper end of the stepwise protocol, where lower-energy shocks were ineffective. The split is also clinically meaningful, as European Resuscitation Council 2025 guidelines recommend 120-200 J biphasic energy, so cases needing only 40 J differ in management from those approaching guideline-level energy; the Extra Trees Classifier subsequently confirmed the dichotomy's discriminative validity. Models evaluated were Logistic Regression, Decision Trees, Random Forest, Extra Trees Classifier, Support Vector Machines, and XGBoost, with grid-search hyperparameter tuning and a 90% training / 10% test split. Internal validation used bootstrap resampling (10,000 replicates) and 10-fold cross-validation, to prevent information leakage from repeated measurements, partitioning and cross-validation were performed at the animal level. Model-based feature importance supported interpretability.

3.3 Study 2: Meteorological Associations with OHCA Incidence

3.3.1 Study Design and Data Sources

A population-based time-series analysis was conducted utilizing the HNAS registry from November 1, 2018, to December 31, 2023. OHCA cases were identified from the database using standardized emergency response codes with daily aggregation by occurrence date. Weather and air quality data were obtained from the Hungarian Meteorological Service as daily national averages.

During the study period, 132,065 OHCA cases were recorded. The analysis was stratified by COVID-19 phase based on healthcare-utilization patterns and national emergency declarations [56, 57]: pre-pandemic (before 3 March 2020), acute (4 March-31 December

2020), and post-acute (from 1 January 2021). To minimize confounding from pandemic-related mortality excess and system disruption, the acute period was excluded, leaving 114,830 cases across 1,584 days.

Seasonal classifications followed established cardiovascular epidemiological conventions [26], with winter defined as October through March and summer encompassing April through September.

3.3.2 Meteorological Parameters and Statistical Analysis

Primary meteorological parameters included daily average temperature (degrees Celsius), daily maximum temperature change, Air Quality Index (AQI), wind speed (meters per second), diurnal temperature range (DTR), atmospheric pressure (hectopascals), weather index (WEI), relative humidity (RH, percentage), and global radiation sum (joules per square centimeter). Additional day-to-day difference variables were calculated for AQI, wind speed, atmospheric pressure, WEI, and relative humidity (RH).

Missing data were handled using a complete-case approach for all parameters except temperature. For temperature, where missingness was minimal (less than 0.2% of observations), missing values were imputed using the median daily temperature to preserve continuity of the time series.

Meteorological parameters were screened for multicollinearity by VIF; WEI and global radiation sum (VIF > 10) were excluded for stability and interpretability. Analyses included 1,584 days after COVID-period exclusion; temporal lag analysis used 1,581 days (3-day maximum lag), and machine-learning models required complete feature matrices totaling 1,526 days.

Primary analysis used negative binomial regression with a logarithmic link to model daily OHCA counts, with temporal lag analysis incorporating exposures 0-3 days before occurrence [58-60]. Univariate models assessed individual parameters and multivariate models all retained parameters simultaneously. Incidence rate ratios were reported with 95% confidence intervals (significance $p < 0.05$), and Bonferroni correction was applied to the three seasonal comparisons (adjusted alpha = 0.017).

Extreme OHCA days were identified using rolling 30-day z-score methodology. Extreme days were defined as those with a z-score exceeding 1.28 or below -1.28 (top and bottom 10th percentiles), representing high- and low-OHCA incidence days, respectively.

Meteorological conditions on extreme days were compared to assess weather patterns associated with elevated CA occurrence.
To characterize meteorological conditions associated with extreme OHCA days, joint distributions of key meteorological variables were visualized using two-dimensional Gaussian kernel density estimation. A fixed bandwidth (0.4) was applied, and density ratio maps were used to compare the probability density of extreme (high-incidence) days against all eligible days to identify over-represented meteorological combinations.

3.3.3 Machine Learning Validation

XGBoost regression models were developed to predict daily OHCA counts. Two model variants were evaluated: a meteorological-only model including all weather parameters with temporal lags, and an enhanced model incorporating meteorological parameters plus 1-7 day antecedent OHCA occurrences. Feature engineering included lag features for meteorological parameters over 0-3 days and historical OHCA patterns over 1-7 days prior.
SHAP (SHapley Additive exPlanations) analysis [61] was performed to assess model interpretability, quantify individual feature contributions, determine the direction and magnitude of influence, and confirm parametric regression findings. Model performance was evaluated using the coefficient of determination, mean squared error, and root mean squared error metrics on holdout test datasets. All analyses were implemented in Python (version 3.9) using libraries including pandas, scikit-learn, XGBoost, statsmodels, and SHAP for model interpretability assessment.

3.4 Study 3: Urban-Rural Disparities in OHCA Outcomes

3.4.1 Study Design and Patient Population

This population-based, retrospective observational study analyzed all OHCA cases in Hungary from January 2018 to December 2023. Data were obtained from the HNAS registry. The study was conducted and reported in accordance with the STROBE guidelines for observational studies [62].
A total of 130,258 OHCA cases were analyzed, classified as urban (n = 91,341) or rural (n = 38,917) using Hungarian national administrative categories [63]. The primary

outcome was on-scene return of spontaneous circulation. All adult OHCA cases (≥18 years) attended by EMS during the study period were eligible for inclusion. Cases related to self-harm or trauma, cases where survival outcome was not recorded, and cases with EMS response times exceeding 120 minutes were excluded.

3.4.2 Variable Definitions and Statistical Methods

Primary exposure was urban versus rural location based on national administrative categories. Key covariates included demographic variables (age, sex), arrest characteristics (etiology, initial cardiac rhythm, witness status, location), EMS system factors (response time, time of day), bystander interventions (CPR provision, AED use), and EMS interventions (advanced airway management, mechanical chest compression device use).

Arrest etiology was classified on scene by the attending EMS personnel following standardized HNAS protocols, integrating clinical presentation, circumstances of the arrest, and available medical history into four categories. Cardiac denotes arrests attributable to a primary cardiac cause (for example, acute coronary syndrome, primary arrhythmia on a known cardiovascular background, or decompensated heart failure). Non-cardiac denotes an evident non-cardiac cause (such as intoxication, drowning, airway obstruction, traumatic haemorrhage, or anaphylaxis). Internal medical disease denotes an advanced underlying medical condition (such as terminal malignancy, end-stage chronic obstructive pulmonary disease or pulmonary fibrosis, or severe non-cardiac sepsis). Unknown is a defined clinical category – not missing data – applied when the available information does not permit unambiguous assignment despite systematic assessment. Cases witnessed by medically trained persons included on-duty EMS personnel, physicians, nurses, or other certified healthcare professionals.

Continuous variables were assessed for normality (histograms, Q-Q plots) and presented as mean ± standard deviation or median with interquartile range as appropriate; categorical variables as frequencies and percentages. Comparisons used the Mann-Whitney U test (continuous) and chi-square test (categorical). Univariable and multivariable logistic regression used variables of established clinical relevance, with VIF for multicollinearity [64, 65]. Owing to centralized, nationally standardized collection, missingness in key variables was minimal; analyses were therefore complete-case, and the Unknown etiology category defined above is a substantive classification, not missing data.

3.4.3 Propensity Score Matching and Sensitivity Analyses

Propensity score matching used a 1:1 nearest-neighbor approach with a 0.2 standard-deviation caliper. Bystander-witnessed status and arrest etiology were exact-matched (greatest confounding potential and clinical importance), and age was exact-matched by individual year; initial rhythm was not exact-matched, to preserve sample size for rhythm-specific subgroups. Standardized mean differences assessed covariate balance before and after matching.

Propensity score matching performance was evaluated by examining standardized mean differences for all covariates before and after matching, values below 0.1 were prespecified to indicating adequate balance. Treatment effect estimates were obtained in the matched cohort using appropriate regression models accounting for the matched design.

Sensitivity analysis modeled EMS response time continuously using natural cubic splines (degrees of freedom = 3) with an urban-rural spline interaction term to explore effect modification across the response time spectrum, avoiding information loss inherent in categorical approaches. Likelihood-ratio testing was used to compare models with and without interaction terms.

Clinical subgroup analyses were performed stratified by initial cardiac rhythm (shockable versus non-shockable), bystander witness status (witnessed versus unwitnessed), arrest etiology (cardiac versus non-cardiac), age groups, and location of arrest (home, public, other). Sensitivity analyses using varying caliper widths (0.1 to 0.25 standard deviations) and alternative model specifications confirmed robustness of findings.

3.4.4 Model Performance and Validation

Model discrimination was quantified using the area under the receiver operating characteristic curve with 95% confidence intervals. Internal validation was performed using repeated 10-fold cross-validation (5 repetitions) and bootstrap validation (1,000 iterations) to assess optimism and generalizability. Calibration was evaluated using calibration plots and the Hosmer-Lemeshow goodness-of-fit test. Predefined diagnostics included subgroup model analysis and evaluation of model stability across urban and rural strata.

Model interpretability analyses were performed to characterize the relative contribution of predictors to outcome probability, including model-based importance measures and SHAP-based analyses. Receiver operating characteristic curves, calibration plots, and additional diagnostic outputs were generated for the overall cohort and for urban and rural subgroups.

Statistical analyses were performed in Microsoft Visual Studio Code (version 1.99.0-insider) using Python (version 3.8) and pandas, numpy, scikit-learn, statsmodels, matplotlib, seaborn, and scipy libraries.

4. Results

4.1 Defibrillation Threshold Prediction Using Machine Learning

4.1.1 Experimental Dataset Characteristics

Defibrillations were performed on 15 experimental animals, resulting in 2100 shock deliveries. Based on this data, 113 DFT values were determined using an energy-selective stepwise defibrillation protocol. Less than 1% of variables had missing values, assessed individually and considered missing completely at random.

Median DFT was 40.00 J (25th percentile: 20.00 J, 75th percentile: 60.00 J, IQR: 40.00 J) (Table 1).

Table 1. Descriptive statistics of measured parameters (n = 113 DFT determinations from 15 animals).

Values presented as median, 25th and 75th percentiles, and interquartile ranges (IQR). Abbreviations: BE (Base Excess), DFT (Defibrillation Threshold), HCO_3^- (Bicarbonate), Hct (Hematocrit), K^+ (Potassium), Na^+ (Sodium), $PaCO_2$ (Partial Arterial Pressure of Carbon Dioxide), PaO_2 (Partial Arterial Pressure of Oxygen).

Parameter	Median	25th Percentile	75th Percentile	IQR
DFT (J)	40.00	20.00	60.00	40.00
BE (mEq/L)	-4.90	-6.20	-4.30	1.90
$HCO3^-$ (mEq/L)	20.30	18.10	21.80	3.70
Hct (%)	38.40	35.70	40.20	4.50
K^+ (mmol/L)	4.20	3.90	4.50	0.60
Na^+ (mEq/L)	147.00	146.00	149.00	3.00
PaCO2 (mmHg)	38.20	32.10	43.00	10.90
PaO2 (mmHg)	167.20	148.40	183.70	35.30
pH	7.35	7.31	7.38	0.07

4.1.2 Correlational Analysis Between ABG Parameters and DFT

Preliminary scatter plot analysis suggested linear relationships between BE and K^+, as well as between $PaCO_2$ and pH. Wilcoxon rank-sum test for pairwise comparisons between high and low DFT groups (130 J vs 40 J) indicated statistically significant differences in Hct and Na^+ levels ($p \leq 0.01$). No significant differences were observed in $PaCO_2$, PaO_2, pH, K^+, HCO_3^-, and BE between groups. Pairwise relationships between variables were presented in a scatterplot matrix (Figure 4).

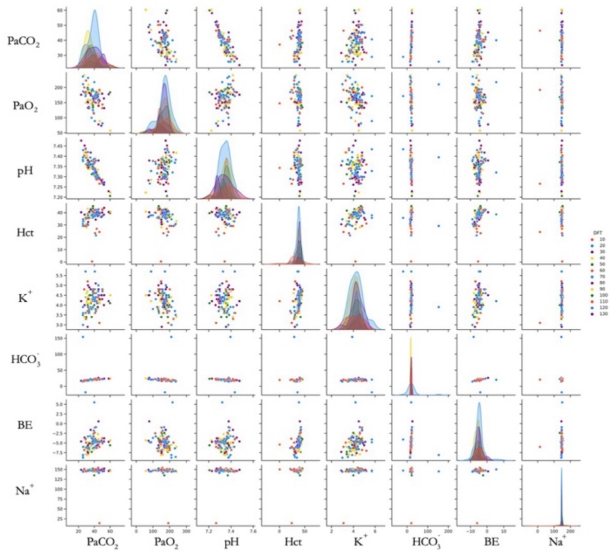

Figure 4. Scatter plot matrix

Abbreviations: BE (Base Excess), HCO_3^- (Bicarbonate), Hct (Hematocrit), K^+ (Potassium), Na^+ (Sodium), $PaCO_2$ (Partial Arterial Pressure of Carbon Dioxide), PaO_2 (Partial Arterial Pressure of Oxygen).

Spearman correlation analysis identified several significant associations with DFT (Table 2). A significant negative correlation was observed between PaO_2 and DFT ($\rho = -0.267$, $p = 0.004$). Positive correlations were found between Hct and DFT ($\rho = 0.247$, $p = 0.008$), and between Na^+ and DFT ($\rho = 0.372$, $p < 0.001$). No significant correlations were detected between $PaCO_2$, K^+, HCO_3^-, or BE and DFT; however, pH showed a modest negative correlation ($\rho = -0.2117$, $p = 0.024$).

Table 2. Spearman's correlation coefficients between ABG parameters and defibrillation threshold (DFT) (n = 113 determinations).

Statistically significant correlations ($p < 0.05$) are indicated in bold. Abbreviations: BE (Base Excess), DFT (Defibrillation Threshold), HCO_3^- (Bicarbonate), Hct (Hematocrit), K^+ (Potassium), Na^+ (Sodium), $PaCO_2$ (Partial Arterial Pressure of Carbon Dioxide), PaO_2 (Partial Arterial Pressure of Oxygen).

Parameter	**Spearman Correlation with DFT**	**p-Value**

BE	−0.0371	0.696
HCO_3^-	0.0339	0.722
Hct	**0.2475**	**0.008**
K^+	0.0583	0.539
Na^+	**0.3728**	**<0.001**
$PaCO_2$	0.1246	0.189
pH	**−0.2117**	**0.024**
PaO_2	**−0.2671**	**0.004**

VIF analysis assessed multicollinearity among variables. Moderate collinearity was detected in pH, Na^+, and K^+ (VIF > 5). Features with high correlation and high VIF values were systematically evaluated, and one member of each correlated pair was retained in model training to reduce coefficient inflation and increase model stability.

4.1.3 Machine Learning Model Performance

Among the evaluated machine learning algorithms (see Section 3.2.4), the Extra Trees Classifier emerged as the top-performing model. Ten-fold cross-validation yielded 71 ± 0.59% standard deviation accuracy. Bootstrap resampling with 10,000 replicates yielded an F_1 score mean of 0.82 (SD: 0.10).

Confusion matrix analysis provided detailed assessment of classification performance (Figure 5). In the test set, the confusion matrix showed 3 true positives, 1 false positive, 8 true negatives, and 0 false negatives, yielding an overall accuracy of 83%.

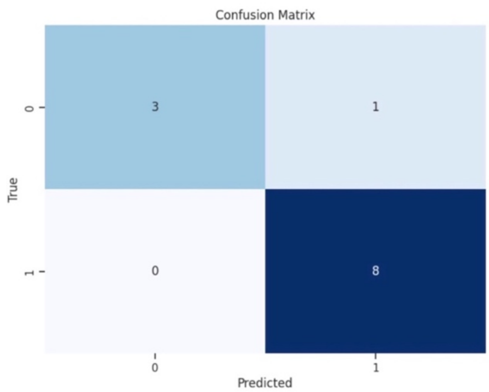

Figure 5. Confusion matrix of the Extra Trees Classifier model for predicting defibrillation energy requirements (N = 113 determinations, 90% training set, 10% test set).

True Positive (TP): 3, False Positive (FP): 1, True Negative (TN): 8, False Negative (FN): 0. Overall accuracy: 83%. Label numbers indicate the DFT classes: Class 0 - 40J, Class 1 - 130J.

4.1.4 Feature Importance Analysis

Feature importance analysis from the Extra Trees Classifier identified the most influential contributors to DFT prediction (Figure 6). The highest-ranked predictors were Hct, PaCO2, PaO2, and Na^+, followed by base excess, K^+, and HCO_3^-.
The top four predictors (Hct, $PaCO_2$, PaO_2, Na^+) accounted for most of the predictive power, spanning haematological (Hct), respiratory gas-exchange ($PaCO_2$, PaO_2), and electrolyte (Na^+) domains. $PaCO_2$ ranked highly despite lacking a significant univariate correlation with DFT, suggesting nonlinear interactions, whereas Hct and Na^+ showed significant positive correlations ($\rho = 0.247$, $p = 0.008$; $\rho = 0.372$, $p < 0.001$) consistent with their importance ranking.

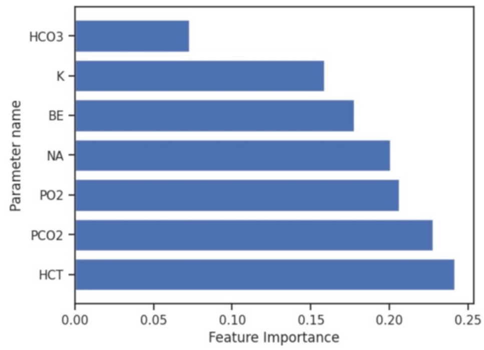

Figure 6. Feature importance values from the Extra Trees Classifier model for predicting defibrillation energy requirements (N = 113 determinations)

Bars represent the relative importance of each parameter in the model's decision-making process. Abbreviations: Hct (Hematocrit), $PaCO_2$ (Partial Arterial Pressure of Carbon Dioxide), PaO_2 (Partial Arterial Pressure of Oxygen), Na^+ (Sodium), BE (Base Excess), K^+ (Potassium), HCO_3^- (Bicarbonate).

4.2 Meteorological Associations with OHCA Incidence

4.2.1 Study Population and Temporal Distribution

The mean age in the cohort was 69.7 ± 14.2 years, and the proportion of male patients was 58.5%. Daily OHCA incidence ranged from 27 to 130 cases, with a mean of 60.9 ± 14.3 cases per day.

4.2.2 Seasonal Variation in OHCA Incidence

Pronounced seasonal variation was observed in daily OHCA incidence (Figure 7). The winter months (October through March; 852 days analyzed) showed higher OHCA rates, with a mean daily incidence of 65.6 ± 15.1 cases. Summer months (April through September; 732 days analyzed) showed a lower incidence, with a mean of 55.7 ± 11.4 cases per day. This difference of 9.9 cases per day (95% CI: 8.6-11.2) represents a 17.8% relative increase in winter OHCA incidence compared to summer ($p < 0.001$).

The seasonal pattern was consistent across study years, with the highest counts in the cold months. The Mann-Whitney U test (U = 434,874, $p < 0.001$) and Kolmogorov-Smirnov test (D = 0.289, $p < 0.001$) remained highly significant after Bonferroni correction (adjusted $\alpha = 0.017$).

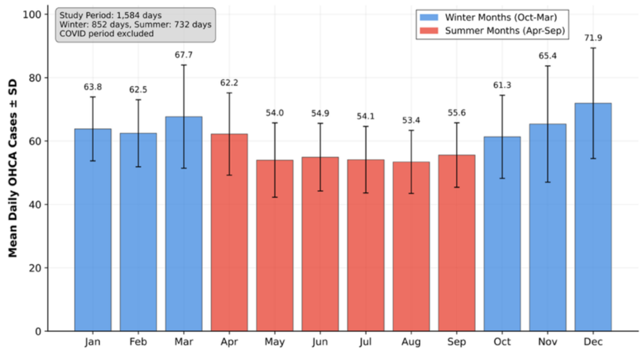

Figure 7. Higher daily OHCA counts are observed across the cold months (November through March), with peaks visible in late autumn and early spring, the analytically defined winter season spans October through March.

Bars represent mean daily cases ± standard deviation per calendar month (winter, October-March, blue, summer, April-September, red). Winter months consistently show higher OHCA incidence, with peaks across the cold months. N = 1584 total days (852 winter days, 732 summer days). Abbreviations: OHCA = Out-of-Hospital Cardiac Arrest; SD = Standard Deviation.

4.2.3 Univariate Meteorological Associations

Negative binomial regression models with logarithmic link functions assessed associations between individual meteorological parameters and daily OHCA counts (Table 3).

Table 3. Univariate and multivariate negative binomial regression results for meteorological parameters and daily OHCA incidence (N = 114,830 cases across 1,584 days).

Results show incidence rate ratios (IRR), 95% confidence intervals, p-values, and percentage change per interquartile range (IQR). Multivariate model: pseudo-R^2 = 0.213, overdispersion parameter α = 0.030; dispersion statistic = 0.943. Abbreviations: AQI = Air Quality Index; CI = Confidence Interval; DTR = Diurnal Temperature Range; IRR = Incidence Rate Ratio; WS = Wind Speed.

Weather Parameter	**Univariate Analysis**			**Multivariate Analysis†**			**% Change per IQR‡**
	IRR	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**	
Primary Meteorological Parameters							
Mean temperature (per 1°C)	0.990	0.988-0.991	<0.001	0.986	0.984-0.987	<0.001	-20.0%
Diurnal temperature range (DTR) (per 1°C)	0.988	0.986-0.991	<0.001	0.998	0.994-1.001	0.185	-1.5%
Wind speed (per 1 m/s)	0.989	0.979-0.999	0.033	0.928	0.912-0.943	<0.001	-7.9%
Barometric pressure (per 1 hPa)	1.000	0.999-1.001	0.840	0.998	0.996-0.999	0.001	-3.8%
Relative humidity (per 1%)	1.003	1.002-1.004	<0.001	0.998	0.997-0.999	<0.001	-3.9%
Air quality index (AQI) (per 1 unit)	0.999	0.998-1.001	0.213	0.994	0.992-0.995	<0.001	-5.0%
Temperature Variability Parameters							
Daily maximum temperature change (per 1°C)	1.001	0.998-1.005	0.408	1.003	0.999-1.007	0.172	+1.0%
Day-to-Day Change Parameters							
AQI daily difference (per 1 unit)	0.998	0.996-1.000	0.113	1.000	0.998-1.002	0.900	+0.1%
Wind speed daily difference (per 1 m/s)	1.006	0.996-1.016	0.230	1.049	1.032-1.066	<0.001	+4.8%
Barometric pressure daily difference (per 1 hPa)	0.998	0.996-1.000	0.061	0.998	0.996-1.001	0.265	-0.8%
Relative humidity daily difference (per 1%)	1.000	0.999-1.001	0.435	1.000	0.999-1.001	0.877	-0.1%

Daily mean temperature showed the strongest univariate association. Each 1°C increase in temperature was associated with a 1.0% decrease in OHCA incidence (IRR = 0.990, 95% CI: 0.988-0.991, $p < 0.001$). Each interquartile range increase in temperature (14.5°C) corresponded to a 13.6% decrease in daily OHCA incidence.

Diurnal temperature range, relative humidity, and wind speed showed weaker but significant univariate associations, whereas barometric pressure and air quality index were non-significant (full results in Table 3).

The WEI and global radiation sum demonstrated VIF values exceeding 10 and were excluded from subsequent multivariate models.

4.2.4 Multivariate Meteorological Associations

A comprehensive multivariate negative binomial regression model included all retained meteorological parameters simultaneously to identify independent associations while controlling for confounding variables (Table 3). The model demonstrated an overdispersion parameter (α) of 0.030, dispersion statistic of 0.943, and pseudo-R^2 of 0.213.

Six parameters demonstrated statistically significant independent associations. Mean temperature remained the dominant predictor. Each 1°C increase in temperature was associated with a 1.4% decrease in OHCA incidence (IRR = 0.986, 95% CI: 0.984-0.987, $p < 0.001$), corresponding to a 20.0% decrease per interquartile range

Wind speed became highly significant in multivariate analysis, with each 1 m/s increase associated with a 7.2% decrease in OHCA incidence (IRR = 0.928, 95% CI: 0.912–0.943, $p < 0.001$). The effect per interquartile range was a 7.9% decrease.

Barometric pressure, relative humidity, and air quality index showed smaller but statistically significant independent associations; daily wind-speed difference was the only parameter positively associated with incidence, and diurnal temperature range was non-significant in the multivariate model (full results in Table 3).

4.2.5 Temporal Lag Structure Analysis

A comprehensive temporal lag analysis examined meteorological exposures from 0 to 3 days before OHCA to identify immediate versus delayed effects (Table 4).

Table 4. Temporal Lag Analysis for Associations Between OHCA and Meteorological Parameters (N = 114,830 cases across 1,584 days)

Temporal lag analysis of associations between meteorological parameters (0-3-day delays) and daily OHCA incidence; each cell is a separate negative binomial model, shown for univariate and multivariate (all-parameter) specifications. Lag 0 = same-day; Lag 1-3 = 1-3 days before onset. N = 1584 days for Lag 0, decreasing to 1581 for Lag 3; weather index and global radiation were excluded (variance inflation factors > 10). Bold values indicate $p < 0.05$. Abbreviations: AQI, air quality index; CI, confidence interval; DTR, diurnal temperature range; IRR, incidence rate ratio; OHCA, out-of-hospital cardiac arrest

Mean temperature demonstrated significant associations at multiple lag periods. In

Parameter	Lag 0 (Same Day)			Lag 1 (1-Day)			Lag 2 (2-Day)		
	IRR	95% CI	p-value	IRR	95% CI	p-value	IRR	95% CI	p-value
Temperature Parameters (Univariate)									
Mean temperature	0.997	0.992-1.002	0.283	0.997	0.990-1.004	0.418	1.003	0.996-1.011	0.427
Diurnal temperature range	**0.993**	**0.990-0.997**	**<0.001**	0.998	0.994-1.003	0.454	**0.995**	**0.991-0.999**	**0.020**
Temperature Parameters (Multivariate)									
Mean temperature	0.993	0.985-1.002	0.144	0.995	0.983-1.007	0.368	1.004	0.992-1.017	0.492
Diurnal temperature range (DTR)	0.995	0.989-1.000	0.059	1.003	0.997-1.009	0.373	0.997	0.991-1.003	0.330
Wind Parameters (Univariate)									
Wind speed	1.000	0.987-1.013	0.957	0.993	0.979-1.007	0.331	**0.984**	**0.970-0.998**	**0.025**
Wind speed daily difference	1.011	0.998-1.023	0.098	1.012	0.998-1.025	0.098	1.002	0.989-1.016	0.756
Wind Parameters (Multivariate)									
Wind speed	**0.977**	**0.966-0.988**	**<0.001**	**0.976**	**0.967-0.984**	**<0.001**	**0.967**	**0.959-0.976**	**<0.00**
Wind speed daily difference	1.002	0.991-1.012	0.793	1.009	0.998-1.020	0.126	1.009	0.997-1.022	0.149
Air Quality Parameters (Univariate)									
Air quality index (AQI)	0.999	0.996-1.001	0.231	1.001	0.998-1.004	0.670	1.001	0.998-1.003	0.713
AQI daily difference	0.999	0.997-1.001	0.225	0.999	0.997-1.001	0.509	1.000	0.998-1.002	0.919
Air Quality Parameters (Multivariate)									
Air quality index	**0.997**	**0.995-0.998**	**<0.001**	**0.998**	**0.997-0.998**	**<0.001**	**0.998**	**0.997-0.999**	**<0.00**
AQI daily difference	0.999	0.998-1.000	0.179	1.000	0.999-1.001	0.886	1.001	0.999-1.002	0.518
Pressure Parameters (Univariate)									
Barometric pressure	0.998	0.996-1.001	0.201	1.001	0.997-1.005	0.554	0.999	0.996-1.003	0.755
Pressure daily difference	**0.997**	**0.995-1.000**	**0.042**	0.998	0.996-1.001	0.158	0.998	0.996-1.001	0.173
Pressure Parameters (Multivariate)									
Barometric pressure	**0.998**	**0.997-0.999**	**0.001**	1.000	0.998-1.001	0.634	1.000	0.999-1.002	0.983
Pressure daily difference	0.998	0.996-1.000	0.073	1.000	0.997-1.002	0.772	1.000	0.997-1.002	0.692

univariate analysis, the 3-day lag showed the strongest association (IRR = 0.991, 95% CI: 0.986-0.996, p < 0.001). In multivariate analysis adjusting for other parameters, the 3-day lag showed a similar trend but did not reach statistical significance (IRR = 0.991, 95% CI: 0.981-1.000, p = 0.062).

Wind speed demonstrated strong protective effects at 3 day-lag period only in the multivariate analysis. The 3-day lagged wind speed showed the strongest association (IRR = 0.959, 95% CI: 0.946-0.972, p < 0.001).

Diurnal temperature range showed predominantly immediate effects, and barometric pressure complex temporal patterns across the lag periods (Table 4).

4.2.6 Extreme-Incidence Analysis

A rolling 30-day z-score approach identified outlier days with unusually high or low OHCA incidence, defined as the top and bottom 10th percentiles (|z| > 1.28). Days classified as high-incidence (top 10%) demonstrated substantially higher daily OHCA counts, with a mean of 79.7 ± 15.3 cases/day (range: 55–130). This represents a 31.9% increase compared with normal-incidence days (mean 60.4 ± 12.2; range: 33–103), corresponding to approximately 19 additional cases/day at the national level.

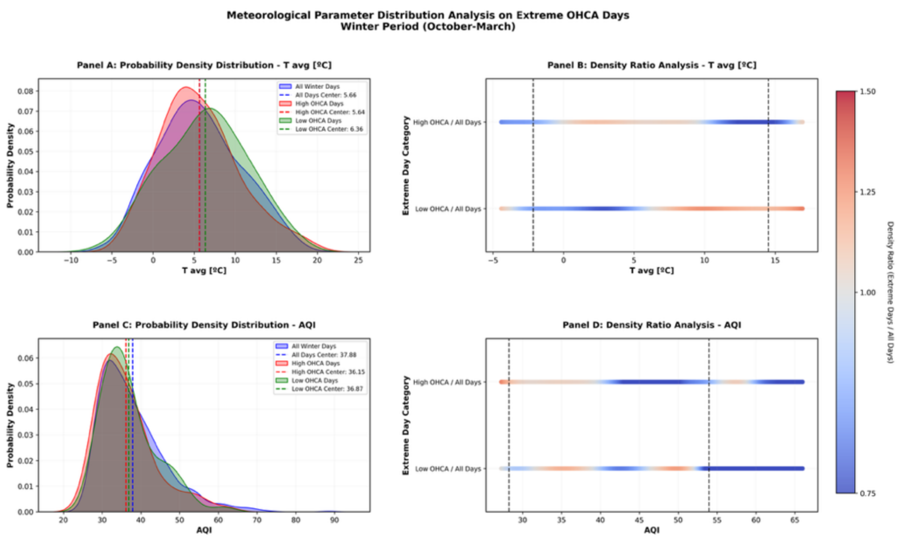

Figure 8. Meteorological Parameter Distributions on Extreme Out-of-Hospital Cardiac Arrest Incidence Days During Winter Months

Distributions of meteorological parameters on extreme-OHCA-incidence winter days (October-March), identified by rolling 30-day z-scores (top and bottom 10th percentiles). Panel A: kernel density of daily mean temperature shows high-OHCA days at colder temperatures (mean 5.64°C) than low-OHCA days (mean 6.36°C), a 0.72°C difference (vertical dashed lines = distribution centres of mass). Panel B: temperature density-ratio heatmap (dashed lines = 5th and 95th percentiles). Panel C: AQI kernel density shows slightly better air quality on high-OHCA days (mean 36.15) than low-OHCA days (mean 36.87). Panel D: AQI density-ratio heatmap. Analysis period November 2018 - December 2023, excluding March 2020 - December 2020. N = 852 winter days; high OHCA days n = 85; low OHCA days n = 85. Abbreviations: AQI, Air Quality Index; OHCA, out-of-hospital cardiac arrest.

Seasonal stratification of extreme days revealed distinct patterns. During winter months (October-March), days with high OHCA incidence occurred at a mean temperature of 5.64°C, compared with 6.36°C for low OHCA incidence days, representing a 0.72°C difference. AQI values on high OHCA days during winter were slightly lower than on low OHCA days (36.15 versus 36.87) (Figure 8).

During summer months (April-September), high OHCA incidence days occurred at mean temperatures of 19.37°C, compared to 19.17°C for low OHCA days (difference: +0.20°C). AQI values were higher during summer high OHCA days (34.06 units) compared to low OHCA days (33.39 units).

Analysis across all seasons combined showed that high OHCA incidence days occurred at mean temperatures of 12.13°C, compared to 12.21°C for low-incidence days (difference: -0.08°C).

4.2.7 Machine Learning Validation

XGBoost regression models provided independent validation of negative binomial regression findings. Two models were constructed to assess predictive capability for operational early warning systems. Model 1, incorporating meteorological parameters only, achieved $R^2 = 0.22$ with a root mean squared error of 13.2 cases per day. Model 2, enhanced with antecedent OHCA data by including OHCA cases from the previous 1-7 days as additional features, achieved improved performance with $R^2 = 0.50$ and Root Mean Squared Error (RMSE) of 10.1 cases per day. This model explained 50% of the variance and reduced prediction error by 23% compared to meteorological parameters alone.

SHAP analysis provided a model-agnostic interpretability assessment (Figure 9). The feature importance ranking confirmed that temperature was the dominant predictor (highest SHAP value), followed by wind speed (second-highest). Among temporal features, 3-day lag effects ranked highest. Cross-validation results demonstrated stable performance across multiple folds with no evidence of overfitting.

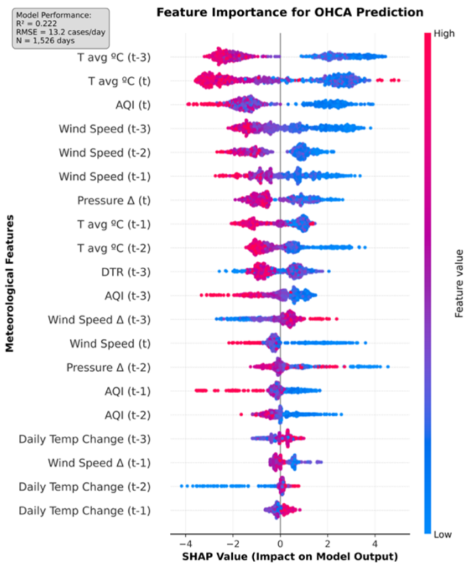

Figure 9. SHAP Value Summary Plot Showing Feature Importance Ranking from the XGBoost Model for Daily OHCA Prediction

Features ranked by importance for predicting daily OHCA incidence, with temperature and wind speed dominant. Each point is an observation, coloured by feature value (red = high, blue = low); horizontal position is the SHAP value (impact on predicted incidence, positive increasing it). Temporal notation: (t) = same-day; (t-1), (t-2), (t-3) = 1-, 2-, and 3-day lags, among which 3-day temperature and wind speed ranked highest. Abbreviations: AQI = Air Quality Index; DTR = Diurnal Temperature Range; OHCA = Out-of-Hospital Cardiac Arrest; RMSE = Root Mean Squared Error; SHAP = SHapley Additive exPlanations.

4.3 Urban-Rural Disparities in OHCA Outcomes

4.3.1 Study Cohort and Geographic Distribution

The dataset comprised 130,258 instances from the HNAS registry between January 2018 and December 2023. Cases were classified as urban (70.1%, N = 91,341) or rural (29.9%, N = 38,917) based on Hungarian national administrative categories.

4.3.2 Overall Urban-Rural Outcome Disparities

The overall ROSC rate across the entire cohort was 9.1%. In urban settings, ROSC rate was 9.4%, compared with 8.3% in rural settings, representing an absolute difference of

1.1 percentage points ($p < 0.001$). Based on the unadjusted descriptive comparison of crude ROSC proportions (9.4% vs 8.3%), the urban ROSC rate was 13.3% higher relative to the rural ROSC rate.

EMS response times differed significantly between urban and rural locations. The median response time was 9.8 minutes (IQR 6.5–15.6) in urban areas versus 14.9 minutes (IQR 11.2–20.1) in rural areas, representing a 52% longer median response time in rural settings ($p < 0.001$).

Baseline characteristics differed systematically by geographical setting. Rural patients were slightly younger (≤65 years: 39.9% rural vs 33.9% urban; $p < 0.001$) and more often male (60.6% vs 57.8%; $p < 0.001$). Arrests occurred predominantly at home in both settings but were more frequent at home in rural areas (81.7% vs 80.0%) and less frequent in public locations (6.9% vs 9.3%; $p < 0.001$). Shockable initial rhythms were less common in rural areas (VF/VT: 13.7% vs 16.1%), whereas asystole was more frequent (71.3% vs 69.4%; $p < 0.001$). Witness status also differed: medically witnessed arrests were more frequent in rural areas (18.9% vs 14.6%), as were non-medical bystander-witnessed arrests (40.4% vs 35.4%; $p < 0.001$). Etiology classification varied, with cardiac etiology reported more often in rural cases (26.0% vs 21.4%) and unknown etiology less frequently (38.5% vs 45.5%; $p < 0.001$).

4.3.3 Univariable and Multivariable Regression Analysis

Unadjusted analysis showed significantly lower odds of ROSC in rural compared to urban areas (OR = 0.88, 95% CI 0.84–0.92, $p < 0.001$), confirming the urban ROSC advantage. Age >65 years was strongly associated with reduced odds of ROSC in univariable analysis (OR = 0.59, 95% CI: 0.57–0.62, $p < 0.001$). Female sex showed a slight reduction in crude odds (OR = 0.94, 95% CI: 0.90–0.97, $p < 0.001$), but became positively associated after multivariable adjustment (aOR = 1.22, 95% CI: 1.17–1.27, $p < 0.001$).

Initial cardiac rhythm was the strongest univariable predictor, with shockable VF/VT, PEA, and bradycardia all showing markedly higher ROSC odds than asystole (full odds ratios in Table 5).

Witness status remained among the strongest predictors of ROSC. Using medically witnessed arrests as the reference category, non-medical bystander-witnessed arrests (OR = 0.59, 95% CI: 0.57–0.62, $p < 0.001$) and unwitnessed arrests (OR = 0.20, 95% CI: 0.19–

0.22, p < 0.001) had substantially lower odds of ROSC. In multivariable analysis, these associations persisted (non-medical bystander-witnessed aOR = 0.56, 95% CI: 0.53–0.59; unwitnessed aOR = 0.46, 95% CI: 0.43–0.49; both p < 0.001).

EMS response time was associated with a progressive decline in ROSC with increasing delays. Response times of 8-15 minutes showed reduced ROSC (OR = 0.72, 95% CI: 0.69-0.75, p < 0.001) compared to ≤8 minutes, with response times >15 minutes showing further deterioration (OR = 0.53, 95% CI: 0.50-0.56, p < 0.001).

Table 5. Overall Cohort – Univariable and Multivariable Logistic Regression Results for Factors Associated with Survival

Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for associations with survival in the total cohort, including patient demographics (age, sex), urbanisation level (urban vs. rural), arrest location, bystander intervention, EMS-assessed initial cardiac rhythm, EMS response time, and time of day.

Category	**Variable Level (Reference)**	**Univariable OR (95% CI)**	**p-value (Uni)**	**Multivariable OR (95% CI)**	**p-value (Multi)**
Patient Variables					
Age	≤65	Ref.	–	–	–
	>65	0.59 (0.57–0.62)	p<0.001	0.64 (0.61–0.66)	<0.001
Etiology	Cardiac	Ref.	–	–	–
	Internal Medical Disease	0.65 (0.62–0.68)	<0.001	0.78 (0.74–0.82)	<0.001
	Non Cardiac	0.81 (0.76–0.87)	<0.001	1.02 (0.94–1.10)	0.64
	Unknown	0.13 (0.12–0.14)	<0.001	0.42 (0.39–0.45)	<0.001
Sex	Male	Ref.	–	–	–
	Female	0.94 (0.90–0.97)	<0.001	1.22 (1.17–1.27)	<0.001
Location & Time					
Arrest Location	Public	Ref.	–	–	–
	Residence (Home)	0.43 (0.41–0.45)	<0.001	0.55 (0.52–0.57)	<0.001
	Other	0.67 (0.63–0.72)	<0.001	0.68 (0.63–0.74)	<0.001
Daytime hours of Arrest	0–8	Ref.	–	–	–
	8–16	1.37 (1.31–1.44)	<0.001	1.07 (1.01–1.12)	0.016
	16–24	1.37 (1.30–1.45)	<0.001	1.08 (1.03–1.15)	0.004
Urbanisation Level	Urban	Ref.	–	–	–
	Rural	0.88 (0.84–0.92)	<0.001	0.83 (0.79–0.87)	<0.001
Bystander Variables					
Bystander Witness	Medical	Ref.	–	–	–
	Non-Medical	0.59 (0.57–0.62)	<0.001	0.56 (0.53–0.59)	<0.001
	None	0.20 (0.19–0.22)	<0.001	0.46 (0.43–0.49)	<0.001
Bystander AED Use	No	Ref.	–	–	–
	Yes, Non-Shockable Rhythm	2.32 (2.07–2.60)	<0.001	1.18 (1.04–1.35)	0.01

	Yes, Shock Delivered	10.51 (9.17–12.05)	<0.001	3.01 (2.57–3.53)	<0.001
Initial Cardiac Rhythm					
Initial Rhythm	Asystole	Ref.	–	–	–
	Bradycardia	4.52 (3.92–5.22)	<0.001	3.54 (3.01–4.17)	<0.001
	PEA	3.38 (3.22–3.54)	<0.001	2.28 (2.17–2.41)	<0.001
	VF/VT	6.22 (5.93–6.52)	<0.001	4.50 (4.27–4.75)	<0.001
EMS Variables					
EMS Total Response Time	≤8 min	Ref.	–	–	–
	8–15 min	0.72 (0.69–0.75)	<0.001	0.75 (0.72–0.79)	<0.001
	>15 min	0.53 (0.50–0.56)	<0.001	0.69 (0.66–0.73)	<0.001
Advanced Airway Use	Advanced Airway	Ref.	–	–	–
	No Advanced Airway	0.09 (0.09–0.10)	<0.001	0.17 (0.16–0.18)	<0.001
Mechanical Chest Compression	No	Ref.	–	–	–
	Yes	1.64 (1.57–1.70)	<0.001	0.89 (0.85–0.93)	<0.001

Multivariable logistic regression incorporating all variables simultaneously revealed that geographic location remained independently associated with ROSC after comprehensive adjustment. Rural locations were associated with a 17% lower ROSC rate (adjusted OR = 0.83, 95% CI: 0.79-0.87, $p < 0.001$) compared with urban settings.

Other independent predictors after adjustment included age >65 years (OR = 0.64, 95% CI: 0.61–0.66, $p < 0.001$). Female sex showed a complete reversal of association direction after adjustment, with women demonstrating 22% higher odds of ROSC (adjusted OR = 1.22, 95% CI: 1.17-1.27, $p < 0.001$) than men.

Initial rhythm remained the strongest independent predictor. VF/VT demonstrated 4.5-fold increased ROSC odds compared to asystole (OR = 4.50, 95% CI: 4.27-4.75, $p < 0.001$), PEA showed 2.3-fold increase (OR = 2.28, 95% CI: 2.17-2.41, $p < 0.001$), and bradycardia demonstrated 3.5-fold increase (OR = 3.54, 95% CI: 3.01-4.17, $p < 0.001$).

EMS response time remained independently associated with outcomes, with response times of 8-15 minutes showing 25% reduced ROSC odds (OR = 0.75, 95% CI: 0.72-0.79, $p < 0.001$) and times >15 minutes showing 31% reduction (OR = 0.69, 95% CI: 0.66-0.73, $p < 0.001$) compared to ≤8 minutes.

Model-based variable influence analysis revealed that initial rhythm had the highest relative importance (100%), followed by witnessed status (78.3%), EMS response time (56.1%), and age (42.7%).

Propensity score matching was performed using nearest-neighbor 1:1 matching without replacement and a caliper width of 0.20. This procedure resulted in 38,734 matched pairs from the 91,341 urban and 38,917 rural cases available for matching, corresponding to a 99.5% matching rate.

Covariate balance assessment demonstrated substantial improvement after matching (Figure 10). Pre-matching standardized mean differences (SMDs) ranged from 0.01 to 0.73. Post-matching, all standardized mean differences were reduced to <0.1, meeting the established threshold for adequate balance. Most variables achieved SMDs <0.05.

Variables with initially large dispersion that were successfully balanced included bystander-witnessed status (pre-matching SMD = 0.73), EMS response time (SMD = 0.55), age (SMD = 0.42), and home versus public location (SMD = 0.39). Post-matching, these variables demonstrated substantial balance improvement, though EMS response time retained some residual imbalance.

In the matched cohort analysis, urban location remained significantly associated with higher ROSC (OR = 1.26, 95% CI: 1.20-1.32, $p < 0.001$), corresponding to a 26% higher odds of ROSC in urban settings.

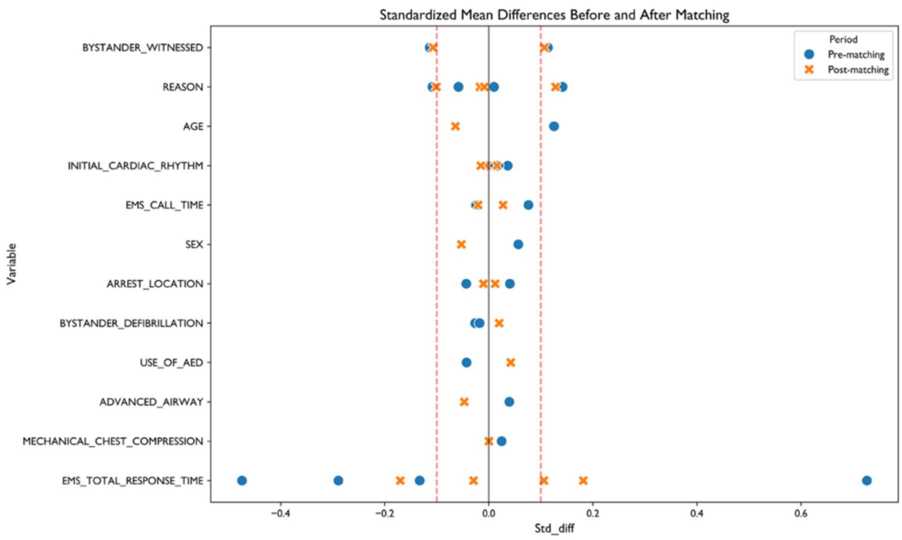

Figure 10. Love plot presenting standardized mean differences (SMD) for baseline characteristics before and after propensity score matching in urban and rural OHCA cohorts

Blue circles = pre-matching standardized mean differences (SMDs); orange crosses = post-matching SMDs; dashed lines at ±0.1 mark the acceptable-balance threshold. Substantial pre-matching imbalances (bystander-witnessed status, EMS response time, age, initial cardiac rhythm, arrest location) were reduced below 0.1 for most covariates after matching, indicating successful adjustment; EMS response time retained some residual imbalance.

4.3.4 Model Performance and Validation

Model performance evaluation demonstrated excellent discrimination. The multivariable model achieved an area under the receiver operating characteristic curve (AUC) of 0.856 (95% CI: 0.853-0.860) for the unmatched dataset and 0.845 (95% CI: 0.842-0.850) for the matched cohort. Bootstrap validation yielded an optimism-corrected AUC of 0.764 (95% CI: 0.760-0.769), confirming robust generalizability with minimal overfitting (optimism of 0.00009). Cross-validation AUC values were 0.856 for the unmatched dataset and 0.845 for the matched cohort.

Model calibration was assessed using the Hosmer-Lemeshow test, which yielded a non-significant result ($p = 0.218$), confirming that predicted probabilities matched observed outcomes. Calibration plots showed close agreement with the ideal diagonal line, though some deviation was observed in the higher-probability range (>0.7), where predictions slightly overestimated actual outcomes.

Sensitivity analyses using varying caliper widths (0.10, 0.15, 0.20, 0.25) yielded comparable results. AUC varied slightly across caliper settings, ranging from 0.842 to 0.850. Odds ratios for urban versus rural ROSC remained similar across all specifications.

4.3.5 Response Time Threshold Analysis

Continuous modeling of EMS response time using natural cubic splines revealed that the urban-rural ROSC disparity varied substantially across the response time spectrum (Figure 11).

For response times ≤8 minutes, urban settings demonstrated markedly superior outcomes, with ROSC rates of 13.2% compared to rural settings at 8.7%, an absolute difference of 4.5 percentage points. The odds ratio of 1.59 (95% CI: 1.44-1.76, $p < 0.001$) indicates 59% higher odds of ROSC in urban areas for rapid responses.

For response times of 8-15 minutes, urban ROSC remained higher (10.3% versus 9.1%), with an absolute difference of 1.2 percentage points and OR of 1.14 (95% CI: 1.05-1.25, $p = 0.002$).

For response times >15 minutes, the urban-rural difference became non-significant, with the odds ratio approaching 1.0.

Continuous spline analysis revealed a non-linear relationship between response time and ROSC, with the steepest decline occurring during the first 10 minutes. The urban-rural gap was largest at the 5-minute threshold, with an OR of 2.37 (95% CI: 1.87-3.00) declining progressively to an OR of 1.42 (95% CI: 1.28-1.58) at 10 minutes and an OR of 1.14 (95% CI: 1.05-1.25) at 15 minutes (Figure 12).

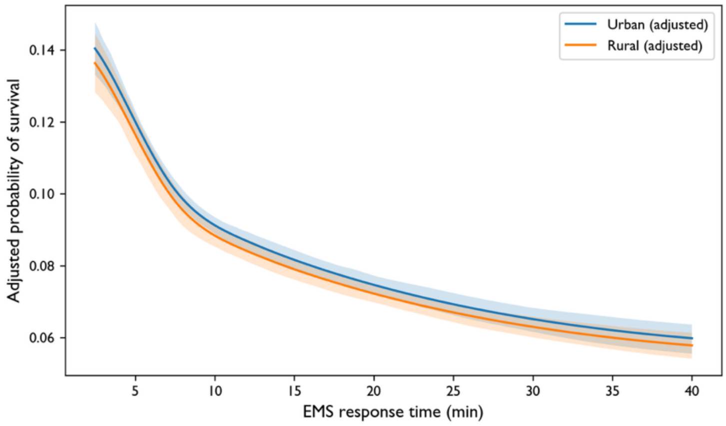

Figure 11. Adjusted Probability of ROSC by EMS Response Time Using Natural Cubic Splines

Adjusted ROSC-probability curves by urban and rural location (natural cubic splines, degrees of freedom = 3) with 95% confidence intervals, showing the dose-dependent decline with increasing EMS response time. The rural×response-time interaction was significant (likelihood-ratio test χ^2 = 54.08, degrees of freedom = 6, $p < 0.001$), confirming that urban-rural differences vary across the response-time spectrum; the urban advantage is greatest at short response times and attenuates with longer delays.

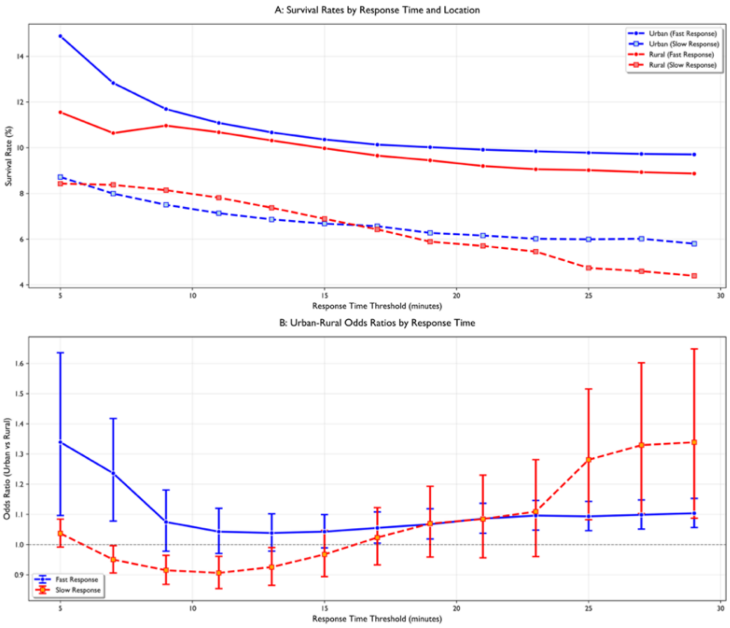

Figure 12. Response time threshold analysis showing urban-rural differences in ROSC across clinically relevant EMS response time cut-offs

Panel A (survival rates): at each response-time threshold (5, 8, 10, 15, 20, and 30 minutes), patients are split into fast (≤ threshold) and slow (> threshold) groups. Fast responses yield higher survival in both settings, more so in urban areas; at ≤5 minutes urban survival reaches approximately 23% versus approximately 12% rural (urban fast 10-23%, slow 7-10%; rural fast 8-12%, slow 4-8%). Panel B (urban-rural odds ratios): for fast responses the urban advantage is largest at 5 minutes (OR = 2.37, 95% CI 1.87-3.00) and declines to OR = 1.22 (95% CI 1.15-1.31) at 30 minutes; for slow responses it is minimal early (OR = 1.20 at 5 minutes) but grows to OR = 2.13 (95% CI 1.78-2.54) at 30 minutes. Urban settings thus retain an advantage across all response times - at short delays likely via more experienced providers and coordination, at long delays via greater availability of advanced life-support resources.

4.3.6 Subgroup Analyses

Subgroup analysis assessed heterogeneity of the urban-rural disparity across clinically relevant patient and arrest characteristics (Figure 13 and Table 6).

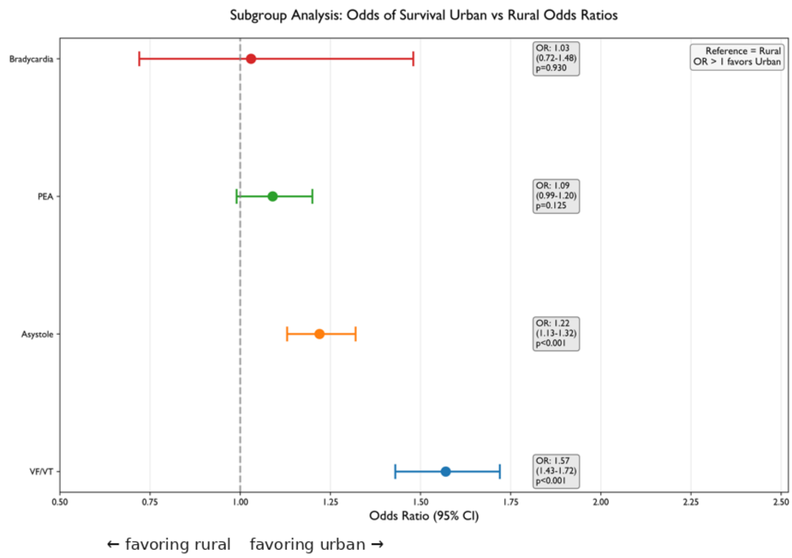

Figure 13. Forest plot showing odds ratios for ROSC by initial cardiac rhythm, comparing urban and rural settings

The vertical dashed line at OR = 1.0 indicates equal odds between settings, whereas OR > 1.0 indicates better ROSC in urban OHCA. The highest urban advantage was observed in VF/VT (OR = 1.57, 95% CI 1.43-1.72, $p < 0.001$), moderate but significant advantage in asystole (OR = 1.22, 95% CI 1.13-1.32, $p < 0.001$), slight advantage in bradycardia (OR = 1.03, 95% CI 0.72-1.48, p = 0.93), and no significant advantage in PEA (OR = 1.09, 95% CI 0.99-1.20, p = 0.12). Error bars represent 95% confidence intervals.

Table 6. Sensitivity Analysis Results by Subgroup

Sensitivity analysis by subgroup, showing N_total, N_urban, N_rural, ROSC percentages and differences, odds ratios with 95% confidence intervals, and p-values (significant values bold). The largest urban advantage was in VF/VT (OR = 1.57), cardiac etiology (OR = 1.35), medical-witnessed arrests (OR = 1.31), and younger patients (OR = 1.30); unwitnessed arrests showed no difference (OR = 1.00). Abbreviations: CI = Confidence Interval; OR = Odds Ratio; PEA = Pulseless Electrical Activity; VF/VT = Ventricular Fibrillation/Ventricular Tachycardia

Subgroup (Variable)	Subgroup Level	N_total	N_urban	N_rural	Urban Survival (%)	Rural Survival (%)	Survival Diff (%)	Odds Ratio (95% CI)	p-value
Initial Cardiac Rhythm	**VF/VT**	9166	4662	4504	30.2	21.63	8.58	1.57 (1.43–1.72)	**< 0.001**
	PEA	12354	6095	6259	15.93	14.83	1.1	1.09 (0.99–1.20)	0.12
	Asystole	55193	27602	27591	5.53	4.58	0.95	1.22 (1.13–1.32)	**< 0.001**

	Bradycardia	755	375	380	20.27	19.74	0.53	1.03 (0.72–1.48)	0.93
Cardiac Arrest Reason (Etiology)	**Cardiac**	21356	11386	9970	17.81	13.79	4.02	1.35 (1.26–1.46)	**< 0.001**
	Non-Cardiac	4698	2342	2356	13.19	12.95	0.25	1.02 (0.86–1.21)	0.85
	Internal Disease	23262	11838	11424	10.74	10.65	0.08	1.01 (0.93–1.10)	0.85
	Unknown	28152	13168	14984	2.84	2.29	0.55	1.25 (1.08–1.45)	**0.01**
Bystander Witness	**Medical-witnessed**	15941	8623	7318	18.43	14.73	3.7	1.31 (1.20–1.42)	**< 0.001**
	Non-Medical	32263	16706	15557	11.23	9.97	1.26	1.14 (1.06–1.23)	**< 0.001**
	None	29264	13405	15859	3.86	3.85	0	1.00 (0.89–1.13)	1.00
Age	**≤ 65**	32518	17100	15418	13.42	10.68	2.74	1.30 (1.21–1.39)	**< 0.001**
	> 65	44950	21634	23316	7.8	6.83	0.97	1.15 (1.07–1.24)	**< 0.001**

Across subgroups, the urban advantage concentrated in the most time-critical, salvageable presentations (full results in Table 6 and Figure 13): it was greatest for shockable VF/VT (OR = 1.57), cardiac etiology (OR = 1.35), medically witnessed arrests (OR = 1.31), and younger patients (OR = 1.30), and absent for unwitnessed arrests (OR = 1.00) and non-cardiac etiology (OR = 1.02).

5. Discussion

5.1 Summary of Principal Findings

This thesis examined OHCA determinants across micro (individual/physiological), meso (geographic/system), and macro (environmental/temporal) levels, providing a comprehensive understanding of factors influencing OHCA incidence and outcomes in Hungary.

At the micro-level, arterial blood gas parameters - particularly hematocrit, serum sodium, and arterial oxygen tension - were significantly associated with the defibrillation energy requirement, and a machine-learning classifier distinguished cases requiring higher energy with high accuracy and high precision in the higher-energy category.

At the macro-level, lower ambient temperature was associated with higher daily OHCA incidence, with a delayed multi-day (three-day lag) effect consistent with cumulative cold stress, and extreme-incidence days clustered under colder conditions.

At the meso-level, urban location was associated with higher odds of on-scene ROSC after propensity score matching, alongside substantially longer rural EMS response times, and the urban advantage was concentrated in time-sensitive cases with shockable rhythms and short response times.

These findings demonstrate that OHCA outcomes are determined by factors operating at multiple analytical levels. While modifiable determinants such as emergency response times and resource distribution offer direct intervention opportunities, unmodifiable factors like extreme meteorological conditions can be leveraged through predictive early warning systems to enable proactive organizational measures including enhanced staffing, public advisories, and targeted prevention strategies during high-risk periods.

5.2 Defibrillation Threshold Prediction Using Machine Learning

5.2.1 Comparison with Existing Literature

The findings extend established understanding that electrical factors alter transmembrane potential and tissue refractoriness [18, 25, 66], a relationship governed by chronaxie and rheobase (the minimum stimulus intensity for successful defibrillation, and the pulse duration at twice the rheobase, respectively) [66]. This study extends these principles by showing that physiological parameters, particularly ABG values, also significantly modulate defibrillation energy requirements.

Previous DFT studies primarily focused on implantable cardioverter-defibrillator contexts with inconsistent protocols and variable endpoints [43, 44, 67-69], limiting identification of reproducible physiological predictors. This investigation employed a standardized stepwise protocol with consistent energy titration and objective success criteria, enabling precise threshold determination.

Classical correlation and machine learning provided complementary perspectives: correlation revealed significant linear associations for hematocrit, sodium, and PaO_2, while the Extra Trees Classifier captured additional nonlinear and interaction effects. The divergence was clearest for $PaCO_2$, which showed high feature importance despite no significant univariate correlation ($\rho = 0.1246$, $p = 0.189$), indicating predictive value emerging through interactions rather than independent effects, and underscoring the complementary roles of interpretable testing and flexible modeling.

5.2.2 Physiological Mechanisms

The mild-to-moderate positive correlation between hematocrit and DFT ($\rho = 0.247$, $p = 0.008$) suggests that elevated red blood cell concentration increases the energy required for defibrillation. Higher hematocrit increases blood viscosity, potentially altering electrical current distribution through cardiac tissue and thoracic cavity while increasing transthoracic impedance, requiring higher applied energy to achieve the transmyocardial current necessary for successful defibrillation.

The statistically significant, moderate-strength positive correlation between serum sodium and DFT ($\rho = 0.372$, $p < 0.001$) represents the strongest physiological association identified among the parameters examined. Sodium serves as one of the primary determinants of cellular membrane potential, with extracellular gradients governing myocardial excitability. Elevated sodium concentrations may stabilize abnormal electrical activity during ventricular fibrillation, thereby increasing the electrical energy required to synchronize myocardial depolarization and terminate fibrillatory activity. This aligns with fundamental principles of cardiac electrophysiology, in which sodium channel dynamics directly influence action potential propagation and responses to external electrical stimuli [70, 71].

The mild-to-moderate negative correlation between partial arterial oxygen pressure and DFT ($\rho = -0.267$, $p = 0.004$) indicates hypoxemia facilitates electrical defibrillation. Reduced oxygen availability alters mitochondrial function and cellular energy metabolism, potentially lowering the electrical threshold required for myocardial depolarization. This suggests aggressive hyperoxia during resuscitation may inadvertently increase defibrillation energy requirements, balanced against the established benefits of adequate tissue oxygenation for post-resuscitation outcomes.

5.2.3 Clinical Applicability and Limitations

Clinical application is constrained to monitored settings where ABG measurements are routinely available: cardiac catheterization laboratories, intensive care units, emergency departments with arterial access, and cardiac surgery operating rooms. Patients suffering ventricular fibrillation or ventricular tachycardia storms requiring multiple shock deliveries could benefit from energy selection guided by blood homeostatic parameters. European Resuscitation Council guidelines currently recommend standardized biphasic energy protocols of 120–200 J for initial defibrillation [11], which serve well for expeditious treatment but do not account for inter-individual physiological variability.

This approach does not apply to basic life support settings, prehospital CA management, or automated external defibrillator deployment where ABG measurements are unavailable. Potential clinical benefit lies in improving first-shock success rates for refractory ventricular arrhythmias in monitored settings, where modest improvements may reduce cumulative myocardial injury from multiple shock deliveries.

These associations were observed within narrow physiological ranges (sodium median 147.0 mEq/L, IQR 3.0; hematocrit 38.40%, IQR 4.50; PaO_2 167.20 mmHg, IQR 35.30; Table 1), which carries two implications. First, the correlations cannot be directly extrapolated to overtly pathological states such as marked hyponatraemia or polycythaemia. Second, the detection of significant associations even across such a restricted range suggests that the true association may be underestimated rather than overstated. These findings are therefore hypothesis-generating and require prospective human validation.

The canine experimental model provides controlled conditions but introduces translational limitations. Significant interspecies differences exist in cardiac electrophysiology, thoracic geometry, and metabolic responses. Human validation studies in appropriate clinical settings are essential before implementation. The sample size of 113 DFT determinations across 15 subjects necessitates expansion to larger, more diverse populations to ensure generalizability.

5.3 Meteorological Factors and OHCA Incidence

5.3.1 Comparison with Existing Literature

The temperature-OHCA relationship (1.4% increase in incidence per 1°C decrease) aligns with international evidence demonstrating that cold is associated with elevated cardiovascular risk [10, 45-47]. Meta-analyses have consistently reported increased cardiovascular events during cold exposure, with effect sizes varying across regions [48, 72]. The 17.8% higher winter incidence in Hungary falls within ranges reported internationally, including Finnish (19.4% winter increase) [26], United States (15–25% variations) [10], and Polish (23.8% winter excess) [45] studies.

The three-day lag structure provides mechanistic insights consistent with cumulative physiological stress rather than immediate triggering. Cold exposure effects operate through multiple temporal mechanisms, including acute sympathetic activation with immediate vasoconstriction and increased cardiac workload, plus delayed inflammatory responses and altered coagulation parameters manifesting over subsequent days [73, 74]. The extreme weather analysis demonstrating 31.9% higher incidence addresses a critical literature gap by providing standardized extreme event characterization. Extreme OHCA burden days showed lower air quality indices (mean 36.15 versus 36.87 on regular days), indicating cold, dry air masses associated with temperature extremes produce better air quality. This suggests that the temperature-OHCA relationship operates independently of air pollution mechanisms, representing a direct meteorological effect rather than a confounded association with particulate matter exposure.

5.3.2 Physiological Mechanisms

Cold exposure activates several pathways that raise cardiovascular risk. Sympathetic activation causes peripheral vasoconstriction, increasing systemic vascular resistance and cardiac afterload while raising heart rate and myocardial oxygen demand [73, 74]. In patients with coronary artery disease, the resulting supply-demand mismatch can precipitate ischemia. Cold also activates inflammatory cascades and shifts haemostasis toward a prothrombotic state, increasing the risk of acute coronary syndrome and plaque rupture [75, 76].

The three-day lag pattern suggests cumulative physiological stress drives the association. Cold stress effects accumulate over days, with sustained sympathetic activation, progressive inflammatory responses, and ongoing hemostatic alterations creating a vulnerable physiological state. This temporal pattern indicates that sustained cold periods pose a greater risk than transient temperature fluctuations.

Beyond temperature, higher wind speed was independently associated with lower OHCA incidence in the multivariable model (IRR = 0.928, 95% CI: 0.912–0.943, $p < 0.001$ per 1 m/s; Table 3). Two mechanisms may act in opposing directions: stronger wind augments convective heat loss and wind-chill, which would be expected to intensify cold-related sympathetic activation, whereas it also improves dispersion of air pollutants (reflected in lower air quality indices), reducing respiratory and cardiovascular risk. The net protective direction observed here suggests the latter may predominate, although the biological basis remains incompletely characterized and this interpretation is hypothesis-generating.

5.3.3 Comparison with Studies Showing Non-linear Temperature-OHCA Relationships

International literature describes J-shaped or U-shaped temperature-OHCA relationships with increased incidence at both extremes [48, 72, 77, 78]. Hungary experiences substantial winter cold but moderate summer temperatures rarely reaching sustained extreme heat levels observed in southern European or subtropical regions, where heat-related OHCA becomes prominent [79, 80]. Linear modeling proved consistent with more flexible nonlinear specifications, including cubic splines and XGBoost, indicating that within Hungary's climate range, linear approximations adequately capture the temperature-OHCA relationship.

The predominantly linear, cold-associated relationship observed in Hungary likely reflects a temperate continental climate, where extreme heat exposure is limited. This finding reflects geographic specificity rather than contradicting broader international evidence. As climate change progresses and extreme heat events become more frequent in Central Europe, future analyses may detect emerging heat-related OHCA manifesting as ascending limb of J-shaped curve.

5.4 Urban-Rural Disparities in OHCA Outcomes

5.4.1 Comparison with Existing Literature

The urban-rural ROSC disparity (OR = 1.26 after propensity score matching) is consistent with international evidence while demonstrating more modest effect size compared to certain registries. Irish data demonstrated nearly 2-fold rural disadvantage in survival to hospital discharge [81], Danish analysis showed 40% lower rural survival [82], and Swedish studies reported persistent geographic disparities [83]. The relatively smaller disparity magnitude in Hungary, despite statistical and clinical significance, likely reflects unified national emergency medical services structure with standardized protocols, equipment, and training across regions.

Hungary's single national EMS provider eliminates organizational heterogeneity and service fragmentation characterizing multi-provider systems, ensuring consistent, regularly supervised and updated clinical protocols, personnel training, equipment standards, and quality assurance mechanisms. However, persistent urban advantage after comprehensive confounding control indicates standardized protocols alone cannot fully compensate for geographic differences in response times, population density, and proximity to advanced care facilities affecting bystander intervention rates.

The crude OHCA incidence captured by the HNAS also exceeds the internationally reported range (67–170 per 100,000 annually; Section 1.1.1). This largely reflects case definition and ascertainment rather than a true excess: the HNAS records every EMS-identified arrest, including non-attempted resuscitations and the full etiological spectrum, whereas many international registries count only attempted or cardiac-etiology arrests, and its centralized national structure minimizes under-reporting. For the same reason, the 9.1% on-scene ROSC rate is not directly comparable with the survival-to-discharge endpoints used by registries such as EuReCa, reflecting endpoint heterogeneity rather than a genuine outcome difference; an Utstein-standardized recalculation enabling direct international comparison is a priority for future work.

The strongest urban advantage in shockable rhythms (VF/VT: OR = 1.57, 95% CI: 1.43–1.72) reflects the time-sensitivity of geographic disparities, as VF/VT deteriorates rapidly to non-shockable rhythms without prompt defibrillation [84, 85]. Non-shockable rhythms showed attenuated or absent advantage: PEA (OR = 1.09, 95% CI: 0.99–1.20, p = 0.12) and bradycardia (OR = 1.03, 95% CI: 0.72–1.48, p = 0.93) showed no significant difference, and asystole only a modest one (OR = 1.22, 95% CI: 1.13–1.32, p < 0.001), consistent with their lesser dependence on rapid defibrillation.

5.4.2 Response Time Analysis

The 52% longer median rural response time (14.9 versus 9.8 minutes) disproportionately impacts most time-sensitive and potentially salvageable CA presentations. Conversely, unwitnessed arrests demonstrated no significant urban-rural difference (OR = 1.00, p = 1.00), as these cases have inherently poor prognosis regardless of location.

Continuous response-time modeling using natural cubic splines revealed important nonlinear patterns and demonstrated how urban-rural disparities vary across the response-time spectrum. For response times ≤8 minutes, urban settings demonstrated markedly superior outcomes (13.2% versus 8.7% ROSC) with OR = 1.59 (95% CI: 1.44–1.76), representing the most pronounced geographic advantage observed. This aligns with international evidence demonstrating that each minute of delay reduces survival odds by approximately 7–10% without effective bystander CPR [19, 86, 87]. The steep decline during the critical first 5–8 minutes means even modest geographic differences translate into substantial outcome disparities.

The attenuated urban advantage at intermediate response times (8–15 minutes: OR = 1.14, 95% CI: 1.05–1.25) and near-elimination at prolonged delays (>15 minutes: OR approaching 1.0) indicate that both settings experience poor outcomes when resuscitation is substantially delayed. This supports the Chain of Survival concept, emphasizing that survival depends on early, rapid, sequential interventions and that prolonged delays diminish the potential benefit of subsequent high-quality care [11, 88].

The paradoxically higher rural survival in the 8–15-minute response time category (9.8% versus 8.5% in urban areas) requires cautious interpretation. Possible explanations include geographic selection bias (different case mix), unmeasured confounding by bystander CPR quality or duration, or differential EMS provider experience levels. This warrants further investigation with more granular data.

Although propensity score matching balanced all covariates to standardized mean differences below 0.10, a residual imbalance persisted for response time. This is expected, because response time is not merely a confounder but a causal mediator of the geographic effect, and over-matching on it would remove part of the very pathway under study. The estimate was nonetheless robust: across caliper widths from 0.10 to 0.25 standard deviations the discrimination remained stable (AUC 0.842–0.850), and the adjusted rural disadvantage persisted in the multivariable model that retained response time as a covariate (adjusted OR = 0.83, 95% CI: 0.79–0.87). The residual imbalance therefore does not materially bias the estimated geographic effect.

5.4.3 Determinants Beyond Response Time

The persistent urban advantage after matching on response time categories and comprehensive patient/arrest characteristics indicates that response time alone does not fully explain geographic disparities. Additional contributing factors likely include variations in bystander CPR quality and duration, differences in the availability of public access defibrillation, variations in EMS providers' experience with CA management, and proximity to advanced cardiac care facilities. The matched analysis controlled for documented bystander CPR but could not assess its quality or duration, which may differ systematically across settings.

The concentration of the urban advantage in the most salvageable presentations – shockable rhythms, short response times, and medically witnessed arrests – is itself informative. If the disparity were driven primarily by hidden confounders such as regional differences in comorbidity, the advantage would be expected to appear in the poorer-prognosis subgroups (older patients, unknown etiology, asystole, unwitnessed arrests); instead, it is absent or attenuated there. This pattern is most consistent with system-level care quality – AED availability, layperson CPR, and concentrated post-resuscitation infrastructure – as the primary driver, rather than population composition. Definitive attribution of long-term benefit will require linkage of the registry to hospital records, which is ongoing work.

The sex-specific findings further illustrate the importance of multivariable adjustment. The crude association of female sex with ROSC was slightly unfavourable (OR = 0.94, 95% CI: 0.90–0.97), yet it reversed to a 22% higher adjusted odds (adjusted OR = 1.22, 95% CI: 1.17–1.27) – a Simpson's-paradox-type effect arising because women presented proportionally more often with non-cardiac or unknown etiologies and non-shockable rhythms. Once etiology, rhythm, age, and witness status are accounted for, an apparent biological advantage emerges; as for the cohort overall, however, this early ROSC advantage may not translate into better long-term survival.

Public access defibrillation programs remain disproportionately concentrated in urban environments [89-91]. International evidence demonstrates that rapid layperson defibrillation with automated external defibrillators substantially improves survival in witnessed CA with shockable rhythms [92-95]. Strategic expansion of rural public access defibrillation, including innovative approaches such as drone-delivered automated external defibrillators or placement in community gathering locations, represents a promising intervention to reduce geographic disparities independently of EMS system improvements.

5.5 Clinical and Policy Implications

The Hungarian National Ambulance Service registry, the shared data source for the meteorological and urban-rural studies, provides a unified national platform for implementing and evaluating the interventions below.

Ranked by implementation feasibility, cost, and expected yield, three intervention priorities emerge. The most readily implementable is a meteorology-based early-warning system (macro-level), which builds on existing forecasting infrastructure at minimal cost. Second is the expansion of rural public-access defibrillation and community CPR training (meso-level), targeting the time-critical, salvageable subgroups in which the urban advantage is greatest. Third, with the longest implementation horizon, is physiology-guided defibrillation energy selection (micro-level), which requires prospective human validation before clinical deployment. These levels are detailed below.

At the macro-level, a meteorological early-warning system is a relatively low-cost, high-impact intervention: the lag patterns give sufficient advance notice for operational planning, integration with existing forecasting infrastructure could trigger automated alerts to EMS, hospitals, and public-health authorities, and public messaging during extreme cold could promote protective behaviour and early symptom recognition.

At the meso-level, reducing disparities requires investment in rural EMS infrastructure: additional ambulances and personnel, expanded public-access defibrillation, community CPR training, and innovations such as drone-delivered defibrillators. Cost-effectiveness analyses should prioritize interventions targeting the time-sensitive, salvageable shockable-rhythm presentations, where rapid intervention yields the greatest survival benefit.

At the micro-level, physiologically guided energy selection requires human validation before deployment. Suitable target populations include catheterization-laboratory PCI patients, ICU patients with refractory ventricular arrhythmias, and cardiac-surgery patients with perioperative VF, for whom ABG data are already available; integrating ABG parameters with defibrillation devices could enable real-time optimization. This must be strictly limited to settings where arterial access and blood-gas data already exist, and under no circumstances should arterial sampling or analysis delay immediate guideline-recommended defibrillation.

From a policy perspective, this thesis demonstrates the value of comprehensive national health data registries in enabling population-level, real data-based research to address critical public health challenges.

5.6 Strengths and Limitations

5.6.1 Methodological Strengths

This thesis demonstrates important methodological strengths. The multi-level analytical framework provides a comprehensive perspective on OHCA determinants, enabling identification of modifiable factors operating across different scales. Integration of multiple methodological approaches, including traditional statistical modeling, machine learning techniques, and advanced causal inference methods (propensity score matching, continuous response time modeling with natural cubic splines), provides robust evidence less susceptible to methodological artifacts.

The DFT study used a standardized protocol with consistent energy titration and objective success criteria, with multiple machine-learning architectures validated by 10-fold cross-

validation and bootstrap resampling. The meteorology study used comprehensive data with minimal missingness and time-series methods accounting for autocorrelation and overdispersion, validated through complementary approaches.
The urban-rural study benefited from nationwide registry data (eliminating selection bias), comprehensive confounding control through multivariable adjustment and propensity score matching, and continuous response-time modeling avoiding categorization loss, the 99.5% matching rate indicates excellent covariate overlap supporting causal inference.

5.6.2 Limitations and Sources of Uncertainty

The DFT study employed canine experimental model, introducing translational uncertainty regarding direct applicability to human patients. Important interspecies differences exist in cardiac electrophysiology, thoracic anatomy, and metabolic responses to ventricular fibrillation. While experimental animal models provide essential controlled conditions for mechanistic investigation, human validation studies in appropriate clinical settings are required. The sample size of 113 DFT determinations necessitates expansion to larger, more heterogeneous populations to ensure prediction model generalizability.
The meteorology study's observational design precludes definitive causal inference despite robust associations and biologically plausible mechanisms. Unmeasured confounding by factors correlated with both weather patterns and OHCA risk (seasonal variation in physical activity, dietary patterns, influenza epidemiology) may influence observed associations. The exclusion of COVID-19 pandemic period (March 2020–December 2020) was necessary to avoid confounding but introduces uncertainty regarding whether temperature associations remained stable during this period. The population-level ecological analysis cannot distinguish individual-level susceptibility factors or attribute causality at the individual patient level.
The urban-rural study's registry design depends on field documentation of variable quality across providers, and the binary urban-rural classification may not capture finer gradations or within-category heterogeneity in remoteness, density, and access. The analysis focused on on-scene ROSC, which provides limited information on longer-term survival and neurological outcome; on-scene ROSC is nonetheless an internationally validated surrogate correlating with downstream outcomes [81, 82], and registry linkage

to hospital records to capture survival to discharge, 30-day survival, and Cerebral Performance Category outcome is a priority for future work. Hospital-level post-resuscitation factors (specialized CA-centre availability, therapeutic hypothermia) were not assessed but likely affect ultimate survival.

The geographic specificity of findings from Hungarian context introduces uncertainty regarding generalizability to other healthcare systems and climate zones. However, consistency of key findings with international evidence (temperature-OHCA associations, urban-rural disparities) supports broader relevance of core conclusions.

5.7 Future Research Directions

Defibrillation Threshold Prediction Using Machine Learning

Priorities include human validation in controlled clinical settings, larger and more diverse cohorts, and additional physiological parameters (lactate, glucose, inflammatory markers), alongside real-time ABG integration with defibrillator systems and decision-support tools with fail-safe mechanisms.

Meteorological Associations with OHCA Incidence

Future extensions include multi-country comparisons of temperature-OHCA heterogeneity, regional Hungarian analyses, and investigation of heat-related OHCA as extreme heat increases. Implementation priorities include evaluating early-warning effectiveness, the cost-effectiveness of weather-responsive EMS staffing, and optimal alert thresholds, plus a formal mediation analysis separating direct thermal effects from seasonal and air-quality pathways.

Urban-Rural Disparities in OHCA Outcomes

Future work should expand outcome measures to include hospital discharge survival, neurological status, and long-term quality-of-life assessment, which would provide a comprehensive understanding of geographic disparities. Intervention priorities include rural public access defibrillation program implementation studies, drone-delivered automated external defibrillator pilots, and community CPR training studies examining whether enhanced bystander intervention compensates for longer EMS response times.

The integrated research raises cross-level questions: whether weather differentially affects urban versus rural incidence, whether physiological parameters vary with environmental conditions, and whether weather-responsive resource allocation reduces disparities during high-risk periods. A further question is whether weather influences the initial rhythm distribution itself – the lower proportion of shockable rhythms in rural arrests (VF/VT 13.7% versus 16.1% in urban areas, $p < 0.001$) may partly reflect longer response times with rhythm degeneration.

Methodological innovations should explore machine learning for cross-level data integration, agent-based models of environmental-system-individual interactions, and causal-inference methods for observational data, ultimately translating findings into evidence-based practice that reduces OHCA burden.

6. Conclusions

6.1 Conclusions Addressing Specific Objectives

This thesis investigated pathophysiology, interventions, prognostic factors, and mortality determinants in conditions requiring cardiopulmonary resuscitation through a comprehensive multi-level analytical framework. The following conclusions directly address the specific objectives established in Section 2.

Objective 1 (MICRO-Level Analysis – Predicting Defibrillation Energy Requirements Using Physiological Parameters):

Arterial blood gas parameters can predict defibrillation energy requirements with clinically meaningful accuracy in controlled clinical environments. The Extra Trees Classifier machine learning model achieved 83% overall accuracy in distinguishing cases requiring higher versus lower initial defibrillation energy, with 100% precision for the higher-energy category and 67% precision for the lower-energy category. Hct, $PaCO_2$, PaO_2, and Na^+ levels emerged as the most significant predictive parameters, demonstrating that rapidly available physiological measurements can inform personalized defibrillation strategies in settings where ABG monitoring is routinely performed, including cardiac catheterization laboratories, ICUs, emergency departments and cardiac surgery operating rooms. The positive correlations observed between Hct and DFT ($\rho = 0.247$, $p = 0.008$), between Na^+ and DFT ($\rho = 0.372$, $p < 0.001$) provide evidence that metabolic and electrolyte status directly influence defibrillation success, supporting the feasibility of physiologically-guided energy selection to optimize first-shock success rates while minimizing unnecessary high-energy exposures.

Objective 2 (MACRO-Level Analysis – Quantifying Meteorological Associations with OHCA Incidence):

Meteorological factors show robust, significant associations with daily OHCA incidence in the Hungarian population, with temperature as the dominant environmental determinant. Each 1°C decrease in daily mean temperature was associated with a 1.4% increase in OHCA incidence (IRR = 0.986, 95% CI: 0.984–0.987, $p < 0.001$), translating to substantial population health impact during seasonal temperature transitions. Winter months demonstrated 17.8% higher OHCA incidence compared to summer months, representing approximately 10 additional daily cases nationally during peak winter periods. Temporal lag structure analysis revealed predictable 3-day-delayed effects, indicating that cardiovascular systems respond to cumulative meteorological stress rather than to immediate environmental changes. Extreme weather days were characterized by 31.9% higher daily OHCA counts, confirming that severe atmospheric conditions substantially increase emergency cardiovascular burden. These findings provide quantitative evidence supporting the development and implementation of weather-based early warning systems, enabling anticipatory emergency medical service resource positioning and targeted prevention strategies for vulnerable populations during high-risk meteorological periods.

Objective 3 (MESO-Level Analysis – Investigating Urban-Rural Disparities in OHCA Outcomes):

Significant and persistent geographic disparities in on-scene return of spontaneous circulation exist between urban and rural settings in Hungary, even after rigorous control for confounding variables. Following propensity score matching that balanced all measured patient and arrest characteristics, urban location remained independently associated with 26% higher odds of achieving return of spontaneous circulation (OR = 1.26, 95% CI: 1.20–1.32, $p < 0.001$). Emergency medical service response times were 52% longer in rural areas (median 14.9 minutes versus 9.8 minutes, $p < 0.001$), resulting in critical delays during time-sensitive interventions. The urban survival advantage was most pronounced in rapid-response scenarios (response times ≤8 minutes: OR = 1.59, 95% CI: 1.44–1.76, $p < 0.001$) and for shockable rhythms (ventricular fibrillation/ventricular tachycardia: OR = 1.57, 95% CI: 1.43–1.72, $p < 0.001$), demonstrating that geographic disparities primarily affect potentially salvageable cases where timely intervention determines outcomes. These findings establish that healthcare system factors—specifically response time differentials and resource distribution patterns—contribute substantially to survival inequities, highlighting the need for targeted interventions to strengthen rural emergency response capabilities, expand public access defibrillation programs in underserved areas, and implement policies that reduce geographic inequities in the chain of survival.

6.2 Integrated Conclusions

Altogether, the three investigations show that OHCA outcomes are shaped by modifiable factors across hierarchical levels: environmental conditions influence when arrests occur (macro), geographic and system factors determine response capability (meso), and individual physiology affects intervention effectiveness (micro). This multi-level framework moves beyond single-factor studies and indicates that reducing preventable mortality requires coordinated interventions spanning prediction, healthcare delivery, and personalized treatment.

The findings support integrated OHCA-reduction strategies acting across all three levels: weather-based early warning for anticipatory resource allocation, rural EMS strengthening and public-access defibrillation to reduce geographic disparities, and physiologically guided defibrillation in appropriate settings. The HNAS registry offers a robust platform to implement and evaluate these interventions, and future work should examine cross-level interactions and extend to long-term survival and neurological outcomes.

7. Summary

This dissertation investigated out-of-hospital cardiac arrest (OHCA) using the nationwide database of the Hungarian National Ambulance Service within an integrated micro-, meso-, and macro-level framework, along three objectives: the relationship between arterial blood gas parameters and defibrillation energy requirement, the association between meteorological factors and OHCA incidence, and urban-rural disparities in survival.

The defibrillation threshold study was performed in an experimental canine model, with 113 determinations in 15 animals. Higher energy requirement was predictable from arterial blood gas parameters with 83% accuracy using an Extra Trees Classifier; the most important, moderately strong predictors were hematocrit ($\rho = 0.247$, $p = 0.008$), sodium ($\rho = 0.372$, $p < 0.001$), and the partial pressure of arterial oxygen ($\rho = -0.267$, $p = 0.004$).

In the meteorological study, 114,830 cases were analyzed between 2018 and 2023. Each 1 °C decrease in temperature was associated with a 1.4% higher daily incidence (IRR = 0.986, 95% CI: 0.984-0.987, $p < 0.001$), with 17.8% higher case numbers during the winter months and 31.9% higher on days of extreme weather. The XGBoost model identified temperature and wind speed as the most important predictors.

In the urban-rural study, 130,258 cases were analyzed (urban 70.1%, rural 29.9%). A significant survival disparity persisted even after propensity score matching (urban 9.4%, rural 8.3%, $p < 0.001$): urban location was associated with 26% higher odds of return of spontaneous circulation (OR = 1.26, 95% CI: 1.20-1.32, $p < 0.001$). The advantage was most pronounced with rapid response (≤8 minutes: OR = 1.59) and shockable rhythms (OR = 1.57).

OHCA outcomes are determined by modifiable, hierarchically interrelated factors. Our findings support the rationale for data-driven, coordinated interventions: meteorological early warning, the expansion of public-access defibrillation programs and community resuscitation training, and the optimization of physiological-parameter-guided, individualized treatment in monitored settings.

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9. Bibliography of the candidate's publications

9.1 Publications related to the PhD thesis

1. **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(11):3879. doi:10.3390/jcm14113879. IF: 2.9, Q1 (Medicine)

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9.2 Publications not related to the PhD thesis

1. Kiss B, **Pál-Jakab Á**, Nagy B, Koós G, Csató G, Pápai Gy, Merkely B, Zima E. Age-Treatment Interactions in Out-of-Hospital Cardiac Arrest: A Nationwide Registry

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