

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

Ph.D. thesis

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1. Introduction

Out-of-hospital cardiac arrest (OHCA) remains one of the most pressing public-health challenges in cardiovascular medicine. Across Europe, the annual incidence ranges from 67 to 170 cases per 100,000 inhabitants, and survival to hospital discharge consistently remains below 10%. Despite decades of standardised resuscitation guidelines, the burden of OHCA continues to be shaped by a complex interplay of environmental, biological, and structural factors that act at distinct levels of the Chain of Survival. Effective improvement of outcomes therefore requires an integrated understanding that extends beyond the moment of arrest itself.

This dissertation investigates OHCA from a three-level perspective, in which each level addresses a different determinant of outcome and a different point along the chain that links population exposure to clinical recovery. The framework is summarised below:

Population-level environmental triggers - the role of meteorological conditions in shaping the daily incidence of OHCA at the national level.

Acute clinical management - personalisation of defibrillation energy through machine-learning prediction of cases requiring a higher defibrillation threshold (DFT) under monitored conditions.

System-level outcome disparities - the impact of geographic context on resuscitation outcomes, examined through a nationwide urban–rural comparison.

The first study addresses the upstream environmental dimension. Although seasonal variation in OHCA is well documented, comprehensive national evidence quantifying the contribution of individual meteorological parameters and their lagged effects has been lacking. Hungary, with a centralised national ambulance service that captures all OHCA events across approximately 9.7 million inhabitants, provides a unique setting for population-based time-series analysis without the selection biases of multi-provider systems.

The second study addresses the acute clinical level. Although early defibrillation is among the strongest predictors of survival from shockable cardiac arrest, the energy requirements for first-shock

success remain individually variable. In monitored environments such as catheterisation laboratories and intensive care units, where arterial blood gas (ABG) measurements are routinely available, identifying patients who will require higher initial energy could reduce time-to-effective-shock and limit unnecessary high-energy deliveries. A controlled animal model permits the systematic determination of true defibrillation thresholds - a measurement that cannot ethically be obtained in human cohorts.

The third study addresses the system level. International evidence suggests that geographic context substantially influences OHCA outcomes, but nationwide analyses from Central-Eastern Europe using uniform data collection and modern confounding control are scarce. Hungary's unified emergency medical service (EMS), with standardised protocols and equipment across all regions, allows the independent effect of urbanisation to be isolated from system-level heterogeneity that confounds many international comparisons.

Taken together, the three studies provide complementary evidence linking environmental triggers, acute clinical decision-making, and structural outcome disparities, and they collectively support the development of weather-informed early-warning systems, individualised defibrillation strategies, and targeted geographic interventions to strengthen the Chain of Survival.

2. Objectives

2.1 Meteorological associations with OHCA incidence

To comprehensively characterise the associations between daily meteorological conditions and the national incidence of OHCA in Hungary using complete population data, to quantify the contribution of individual atmospheric parameters and their temporal lag structures, and to identify weather profiles associated with extreme-incidence days that may inform weather-based early warning.

2.2 Machine-learning prediction of higher defibrillation energy need

To investigate, in a controlled animal model with serial measurement of true defibrillation thresholds, whether routinely available arterial

blood gas parameters can predict cases requiring higher first-shock defibrillation energy, and to develop and internally validate a machine-learning classifier suitable for monitored clinical environments such as catheterisation laboratories and intensive care units.

2.3 Urban-rural disparities in OHCA outcomes

To quantify urban–rural disparities in on-scene return of spontaneous circulation (ROSC) using the complete Hungarian National Ambulance Service registry, to isolate the independent effect of urbanisation through propensity score matching and continuous response-time modelling, and to identify the patient and arrest characteristics associated with the largest geographic survival gap, in order to inform targeted interventions strengthening the rural Chain of Survival.

3. Methods

3.1 Study 1 - National time-series analysis of meteorological factors

A population-based time-series analysis was performed using the complete HNAS registry from 1 November 2018 to 31 December 2023. OHCA cases were identified through standardised emergency response codes, with daily aggregation by event date. Meteorological and air-quality data were obtained from the Hungarian Meteorological Service as nationwide daily averages. After exclusion of the acute COVID-19 disruption phase (4 March 2020 – 31 December 2020), 114,830 OHCA cases over 1,584 days were available for analysis. Of an initial 132,065 OHCA cases, the post-exclusion cohort was used to minimise pandemic-related healthcare and behavioural confounding.

Primary atmospheric exposures included daily mean temperature, diurnal temperature range, wind speed, atmospheric pressure, relative humidity, and Air Quality Index (AQI). Multicollinearity was assessed by variance inflation factors (VIF), and parameters with VIF > 10 (weather index, global radiation sum) were excluded. Negative binomial regression with logarithmic link functions was used as the primary model for daily OHCA counts, with both univariate and

multivariate specifications. Temporal lag analysis incorporated weather exposures from 0 to 3 days prior to OHCA occurrence (1,581 days available). Outlier days with exceptional OHCA case numbers were identified using rolling 30-day z-scores (top and bottom 10th percentiles), and meteorological distributions on these days were assessed using two-dimensional Gaussian kernel density estimation. Independent validation was performed using gradient boosting regression (XGBoost) with SHAP-based feature attribution. Bonferroni correction was applied to seasonal comparison tests (adjusted $\alpha = 0.017$).

3.2 Study 2 - Defibrillation threshold and machine-learning prediction

A controlled experimental study was conducted using 15 healthy male Beagle dogs (10–11 kg) under general anaesthesia, with mechanical ventilation and continuous haemodynamic and ECG monitoring. Pediatric defibrillation pads (8 cm diameter) and biphasic truncated waveform shocks were used. Ventricular fibrillation (VF) was induced by 50 Hz direct current, and the defibrillation threshold (DFT) was determined using a stepwise, energy-selective protocol. A 3-minute haemodynamic stabilisation period followed each successful defibrillation. Across the 15 animals, 2,100 shock deliveries yielded 113 DFT determinations.

Before each defibrillation attempt, arterial blood gas (ABG) parameters were measured: PaCO₂, PaO₂, pH, haematocrit (Hct), sodium (Na⁺), potassium (K⁺), and bicarbonate (HCO₃⁻). Statistical analysis included the Wilcoxon rank-sum test for pairwise comparisons between extreme DFT categories (≤ 40 J vs. ≥ 130 J) and Spearman correlation analysis for ABG–DFT relationships. Multicollinearity was addressed using VIF (parameters with VIF > 5 individually evaluated). Multiple supervised classifiers were trained and tested to predict the high-energy class - including Decision Tree, Random Forest, Extra Trees Classifier, Support Vector Machine, and gradient boosting - with hyperparameter tuning. Model performance was evaluated using overall accuracy, class-specific precision and recall, F1-score, 10-fold cross-validation and bootstrap resampling

with 10,000 replicates. Feature importance was used to identify the dominant predictors.

3.3 Study 3 - Nationwide urban–rural comparison

A retrospective, population-based observational analysis was conducted on all adult OHCA cases (≥ 18 years) attended by the HNAS in Hungary between January 2018 and December 2023, reported according to the STROBE statement. After exclusion of self-harm, trauma, and cases with missing survival outcome or EMS response time exceeding 120 minutes, the analytical cohort comprised 130,258 OHCA cases (99.4% of the original dataset).

Locations were classified as urban (Budapest, cities with county rights, and other towns with city status) or rural (villages and large villages) based on Hungarian administrative categories, corresponding to a population-density gradient from approximately 3,350 inhabitants/km² in Budapest to approximately 45 inhabitants/km² in rural areas. The primary outcome was on-scene ROSC. Univariate and multivariate logistic regression models were developed using clinically relevant variables (age, sex, etiology, initial cardiac rhythm, arrest location, witness status, bystander interventions, advanced airway, mechanical chest compression, time of day, EMS response time). Propensity score matching (PSM) was performed using exact matching on age, witness status, and etiology, with calipers between 0.1 and 0.25 and SHAP-based feature attribution. EMS response time was modelled both categorically (≤ 8 , 8–15, >15 minutes) and continuously using natural cubic splines (3 degrees of freedom) with rural $\times$ spline interaction terms. Model performance was evaluated using AUC with 95% confidence intervals, 10-fold cross-validation with 5 repetitions, bootstrap validation (1,000 iterations), Hosmer–Lemeshow goodness-of-fit testing, and calibration plots.

4. Results

4.1 Meteorological associations with OHCA incidence

Across 1,584 analytical days, the daily OHCA incidence averaged 60.9 ± 14.3 cases (range 27–130). The mean patient age was 69.7 ± 14.2 years, with a male predominance of 58.5%. A pronounced

seasonal pattern was observed: mean daily incidence was 65.6 ± 15.1 cases in winter (October–March, 852 days) versus 55.7 ± 11.4 cases in summer (April–September, 732 days), a difference of 9.9 cases per day (95% CI: 8.6–11.2), corresponding to a 17.8% relative increase in winter (Mann–Whitney $U = 434,874$, $p < 0.001$; Kolmogorov–Smirnov $D = 0.289$, $p < 0.001$ - both significant after Bonferroni correction).

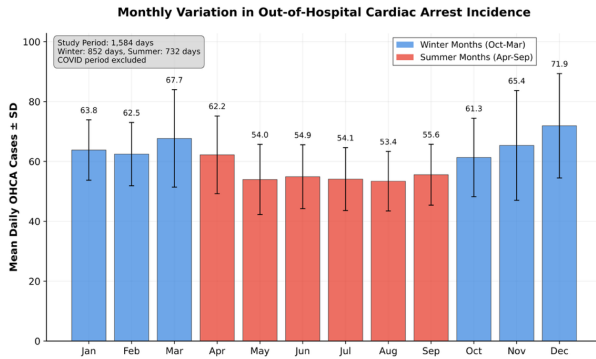


Figure 1. Monthly distribution of daily OHCA incidence demonstrating pronounced seasonal variation across the study period. Bars represent mean daily cases $\pm$ standard deviation for each calendar month; winter months (October–March) shown in blue and summer months (April–September) in red. $N = 1,584$ days (852 winter, 732 summer). Source: Pál-Jakab Á et al. Public Health. 2026;252:106145. CC BY 4.0. Abbreviations: OHCA, out-of-hospital cardiac arrest; SD, standard deviation.

In the multivariate negative binomial model (pseudo- $R^2 = 0.213$; dispersion parameter = 0.943), six independent meteorological predictors emerged. 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, $p < 0.001$), corresponding to a 20.0% reduction per interquartile-range (IQR) increase in temperature. Wind speed showed a strong protective association (IRR = 0.928, 95% CI 0.912–0.943, $p < 0.001$; –7.9% per IQR), while atmospheric pressure (IRR = 0.998, 95% CI 0.996–0.999, $p = 0.001$), relative humidity (IRR = 0.998, 95% CI 0.997–0.999, $p < 0.001$), and AQI (IRR = 0.994, 95% CI 0.992–0.995, $p < 0.001$) showed smaller but significant associations. Daily wind-speed variability was positively associated with OHCA (IRR = 1.049, 95% CI 1.032–1.066, $p < 0.001$)

Lag-structure analysis (0–3 days) revealed that the protective effect of wind speed strengthened with longer lags, peaking at 3 days (IRR = 0.959, 95% CI 0.946–0.972, $p < 0.001$), consistent with cumulative atmospheric circulation effects, while temperature and pressure showed mixed acute and delayed contributions. On extreme high-incidence days (top 10%), daily OHCA averaged 79.7 ± 15.3 cases - a 31.9% increase compared with normal-weather days, equivalent to approximately 19 additional cases per day. During winter, high-incidence days occurred at colder mean temperatures (5.64°C vs. 6.36°C on low-incidence days) and clustered disproportionately at temperatures below 4°C . Independent XGBoost validation ($R^2 = 0.22$ on test data, RMSE = 13.2 cases/day) confirmed temperature and wind speed as the most influential predictors via SHAP analysis.

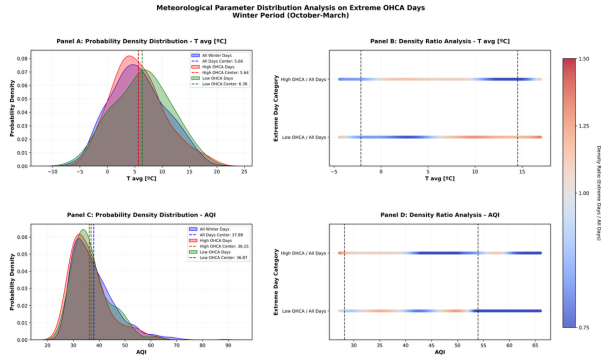


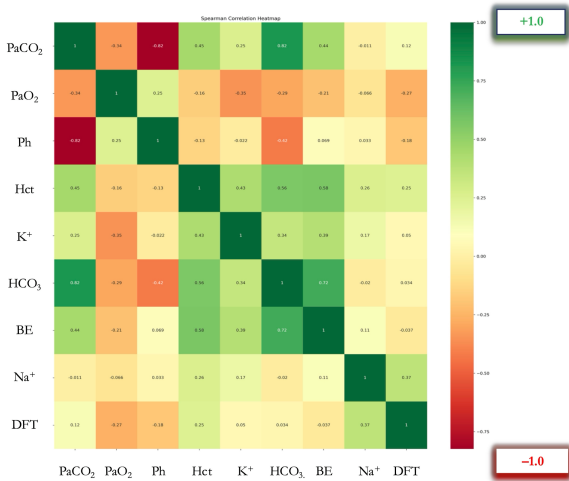
Figure 2. Kernel density estimation of mean temperature and AQI on extreme-incidence days within the winter period. High-OHCA days ($n = 85$) clustered at colder temperatures than low-OHCA days ($n = 85$), with disproportionate density below 4°C . Source: Pál-Jakab Á et al. Public Health. 2026;252:106145. CC BY 4.0. Abbreviations: AQI, Air Quality Index; OHCA, out-of-hospital cardiac arrest.

4.2 Predicting higher defibrillation energy need

In the experimental cohort of 15 male Beagle dogs, 113 defibrillation thresholds were determined from 2,100 protocol-driven shock deliveries, with less than 1% of ABG values missing per variable (missing completely at random). Pairwise comparison between the high-energy group (DFT ≥ 130 J) and the low-energy group (DFT ≤ 40 J) demonstrated significant differences in haematocrit and sodium

(both $p \leq 0.01$), whereas PaCO₂, PaO₂, pH, K⁺, HCO₃⁻, and base excess did not differ significantly between groups.

Spearman correlation analysis showed a significant negative correlation between PaO₂ and DFT ($\rho = -0.267$, $p = 0.004$), and significant positive correlations between Hct and DFT ($\rho = 0.247$, $p = 0.008$) and between Na⁺ and DFT ($\rho = 0.372$, $p < 0.001$). The remaining ABG parameters (PaCO₂, pH, K⁺, HCO₃⁻, base excess) showed no significant correlation with DFT.



*Figure 3. Correlation heatmap of arterial blood gas parameters and defibrillation threshold across 113 determinations from 15 animals. Colour intensity reflects correlation magnitude (red, negative; green, positive). Statistically significant correlations ($p < 0.05$): PaO₂ ($\rho = -0.267$), Hct ($\rho = 0.247$), Na⁺ ($\rho = 0.372$). Source: Pál-Jakab Á et al. *J Clin Med.* 2025;14:3879. CC BY 4.0. Abbreviations: ABG, arterial blood gas; BE, base excess; DFT, defibrillation threshold; HCO₃⁻, bicarbonate; Hct, haematocrit; K⁺, potassium; Na⁺, sodium; PaCO₂/PaO₂, partial arterial pressures of carbon dioxide and oxygen.*

Among the supervised classifiers tested, the Extra Trees Classifier emerged as the best-performing model, achieving an overall accuracy of 83% on the test dataset. For the higher-DFT class (≥ 130 J), precision was 100% with a recall of 75% (F1 = 0.86); for the lower-DFT class (≤ 40 J), precision was 67% with a recall of 100% (F1 = 0.80). Ten-fold cross-validation yielded an accuracy of $71 \pm 0.59\%$ (SD), and bootstrap resampling with 10,000 replicates yielded a mean

F1-score of 0.82 (SD 0.10) and a mean absolute error of 16.19 (SD 9.03), indicating consistent model performance. Feature-importance analysis identified Hct, PaCO₂, PaO₂, and Na⁺ as the dominant contributors to the classifier's decisions.

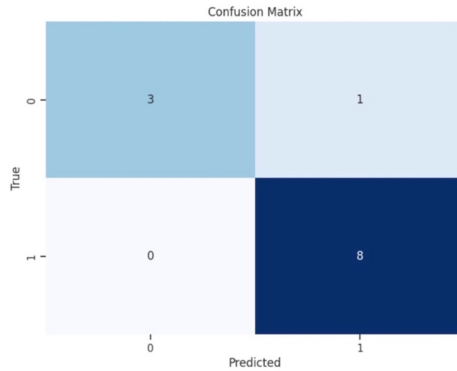


Figure 4. Confusion matrix and feature-importance plot for the Extra Trees Classifier predicting higher defibrillation-energy need. Test set (10%): true positives 3, false positives 1, true negatives 8, false negatives 0; overall accuracy 83%. Hct, PaCO₂, and PaO₂ were the leading contributors. Source: Pál-Jakab Á et al. J Clin Med. 2025;14:3879. CC BY 4.0. Abbreviations: DFT, defibrillation threshold; FP, false positive; FN, false negative; Hct, haematocrit; PaCO₂/PaO₂, partial arterial pressures of carbon dioxide and oxygen; TP, true positive; TN, true negative.

4.3 Urban–rural disparities in OHCA outcomes

The final analytical cohort comprised 130,258 OHCA cases, with 91,341 (70.1%) occurring in urban and 38,917 (29.9%) in rural settings. Mean age was 69.6 ± 14.2 years. Compared with urban cases, rural cases were more often elderly (≥ 65 years: 39.9% vs. 33.9%), male (60.6% vs. 57.8%), and of cardiac etiology (26.0% vs. 21.4%), with a higher proportion of medically witnessed arrests (18.9% vs. 14.6%) - all $p < 0.001$. Most arrests occurred at home (rural 81.7%; urban 80.0%, $p < 0.001$). The median EMS response time was substantially longer in rural areas (14.9 minutes [IQR 11.2–20.1]) than in urban areas (9.8 minutes [IQR 6.5–15.6]; $p < 0.001$) - a 52.0% longer median response time - and the proportion of cases reached within ≤ 8 minutes was 37.6% in urban versus only 8.8% in rural settings.

The overall on-scene ROSC rate was 9.1% (95% CI 8.9–9.2%), with a significant urban–rural disparity (urban 9.4% [95% CI 9.2–9.6%] vs. rural 8.3% [95% CI 8.1–8.6%], $p < 0.001$). In the multivariable model, rural location remained independently associated with lower survival (OR = 0.83, 95% CI 0.79–0.87, $p < 0.001$) after adjustment for patient demographics, arrest characteristics, and EMS variables. The strongest independent predictors of survival were initial rhythm (VF/VT: OR = 4.50, 95% CI 4.27–4.75; bradycardia: OR = 3.54; PEA: OR = 2.28; all $p < 0.001$ vs. asystole) and bystander AED use with shock delivery (OR = 3.01, 95% CI 2.57–3.53). The model demonstrated excellent discrimination (cross-validation AUC = 0.856 [95% CI 0.853–0.860] in the unmatched cohort and 0.845 [95% CI 0.842–0.850] in the matched cohort), with bootstrap-corrected AUC of 0.764 (optimism = 0.00009) and adequate calibration (Hosmer–Lemeshow $p = 0.218$).

Propensity score matching successfully paired 38,734 urban with 38,734 rural cases (99.5% matching rate), with all standardised mean differences below 0.1 after matching. In the matched cohort, urban location remained significantly associated with higher survival (10.28% vs. 8.36%, $p < 0.001$; OR = 1.26, 95% CI 1.20–1.32), corresponding to an absolute survival difference of 1.92 percentage points. Continuous response-time modelling using natural cubic splines confirmed a significant rural $\times$ time interaction (likelihood-ratio $\chi^2 = 54.08$, $df = 6$, $p < 0.001$), with the urban advantage most pronounced at the shortest response times (≤ 5 minutes: OR = 2.37, 95% CI 1.87–3.00) and progressively diminishing thereafter. At the clinically relevant ≤ 8 -minute threshold, urban survival reached 13.2% versus 8.7% in rural settings (OR = 1.59, 95% CI 1.44–1.76, $p < 0.001$). Subgroup analyses showed that the urban survival advantage was largest for shockable rhythms (VF/VT: OR = 1.57, 95% CI 1.43–1.72), cardiac etiology (OR = 1.35, 95% CI 1.26–1.46), and medically witnessed arrests (OR = 1.31, 95% CI 1.20–1.42), whereas no significant difference was observed for unwitnessed arrests.

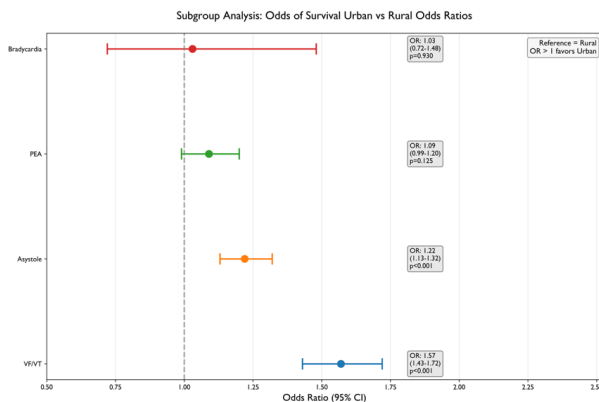


Figure 5: Subgroup forest plot of urban-versus-rural odds ratios across initial cardiac rhythms

Forest plot of subgroup odds ratios (urban vs. rural) for on-scene ROSC, stratified by initial cardiac rhythm. The largest urban advantage was observed for VF/VT (OR = 1.57). Source: Pál-Jakab Á et al. Resuscitation Plus. 2025;26:101108. CC BY 4.0. Abbreviations: OR, odds ratio; PEA, pulseless electrical activity; VF/VT, ventricular fibrillation/tachycardia.

5. Conclusions

The first study established, on the basis of complete national population data, that meteorological conditions are strongly and predictably associated with the daily incidence of OHCA in Hungary. Six independent atmospheric predictors emerged from a multivariate model adjusted for multicollinearity, with daily mean temperature and wind speed dominating the picture: each 1 °C decrease in temperature was associated with a 1.4% increase in OHCA incidence, while wind speed exerted a robust protective effect (−7.9% per interquartile range). Extreme high-incidence days, on which the case load rose by approximately one third, clustered at colder winter temperatures. The 0–3-day lag structure provides a biologically plausible window for weather-based early-warning systems and supports the integration of meteorological data into emergency-response planning.

The second study demonstrated, in a controlled animal model with serial measurement of true defibrillation thresholds, that arterial blood

gas parameters carry meaningful information about the energy required for successful first-shock defibrillation. Hct, Na⁺, and PaO₂ were the parameters most consistently associated with DFT, and a machine-learning classifier (Extra Trees) achieved 83% overall accuracy with 100% precision and 0.86 F1-score for the higher-DFT class, confirmed by 10-fold cross-validation and bootstrap resampling. These findings provide proof of concept that rapidly available physiological data can support individualised defibrillation strategies in monitored environments such as catheterisation laboratories and intensive care units, where ABG measurements are already routine. The model is not intended to replace standardised emergency protocols but to complement them in settings where additional information is accessible at the moment of decision-making.

The third study quantified, in the largest nationwide Hungarian OHCA cohort to date, a persistent urban–rural survival disparity. After comprehensive adjustment, rural location remained independently associated with lower on-scene ROSC odds (OR = 0.83), and propensity score matching of nearly 39,000 pairs confirmed that urban patients retained a 26% higher odds of survival under comparable patient and arrest profiles. Continuous response-time modelling and threshold analyses identified the early response window - and particularly cases with shockable rhythms or witnessed arrests - as the points along the Chain of Survival where the urban advantage is largest, and therefore where rural interventions are likely to yield the greatest gain.

Taken together, the three studies trace a coherent path along the OHCA care continuum, from environmental exposure that determines who suffers an arrest, through the physiological and technical determinants of effective defibrillation, to the structural conditions under which resuscitation actually takes place. Each level identifies an actionable lever: weather-informed surveillance and public-health messaging on high-risk days, individualised defibrillation strategies grounded in ABG data in monitored environments, and targeted strengthening of the rural Chain of Survival - including community-based AED programmes, bystander-CPR education, and EMS dispatch optimisation. The integration of these levels supports the broader translational aim of moving OHCA from a downstream

resuscitation challenge to an upstream, anticipatory model of cardiovascular emergency care.

6. Bibliography of the candidate's publications

6.1 Publications related to the thesis

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SJR: Q1; IF: 3.2

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. *J Clin Med*. 2025;14:3879.

SJR: Q1; IF: 2.9

Pál-Jakab Á, Nagy B, Kiss B, Pápai Gy, Boussoussou N, Merkely B, Constantinovits M, Csató G, Sótónyi P, Szilágyi B, Zima E. Urban–rural disparities in out-of-hospital cardiac arrest outcomes: a nationwide Hungarian study. *Resuscitation Plus*. 2025;26:101108.

SJR: Q1; IF: 2.4

Σ *IF (publications related to the thesis): 8.5*

6.2 Publications not related to the thesis

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SJR: Q1; IF: 2.9

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SJR: Q1; IF: 2.4

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SJR: Q1; IF: 3.0

Σ *IF (publications not related to the thesis): 17.9*

Cumulative impact factor (all publications): 26.4