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Early risk stratification and workflow acceleration in the emergency department: from thermal emergencies to triage-driven decision support

PhD Thesis

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Budapest

2026

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List of abbreviations

5A – Age, Activities of daily living, Arrest, Acidemia, Albumin (severity scale)

ABG – arterial blood gas

AI – artificial intelligence

ATC – Anatomical Therapeutic Chemical (classification system)

AUC – area under the receiver operating characteristic curve

AVPU – Alert, Voice, Pain, Unresponsive (consciousness scale)

CFT – clot formation time

CI – confidence interval

Cliff's δ – Cliff's delta (non-parametric effect size measure)

Cohen's d_z – standardised paired effect size (Cohen's d for dependent samples)

CRP – C-reactive protein

CT – clotting time (viscoelastic testing; used in compound forms ECA-CT and EX-CT)

ECA – ecarin-based assay (ClotPro®)

ECA-CFT – ecarin-based assay clot formation time

ECA-CT – ecarin-based assay clotting time

ECLS – extracorporeal life support

ECMO – extracorporeal membrane oxygenation

ED – emergency department

EHR – electronic health record

ELSO – Extracorporeal Life Support Organization

ERC – European Resuscitation Council

EX-CT – extrinsic pathway clotting time (ClotPro®)

FPR – false positive rate

GCS – Glasgow Coma Scale

GOT/AST – glutamic-oxaloacetic transaminase / aspartate aminotransferase

HCO_3^- – bicarbonate

HELP – prognostic score for non-asphyxia-related hypothermic cardiac arrest after extracorporeal rewarming

HL – Hodges–Lehmann estimator (non-parametric location shift)

HOPE – Hypothermia Outcome Prediction after ECLS (prognostic score)

hs-TnT – high-sensitivity troponin T

ICD-10 – International Classification of Diseases, 10th Revision

ICU – intensive care unit

IQR – interquartile range

ML – machine learning

MSTR – Hungarian Emergency Triage System (Magyar Sürgősségi Triázs Rendszer)

NLR – neutrophil-to-lymphocyte ratio

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

OR – odds ratio

$PaCO_2$ – partial pressure of carbon dioxide in arterial blood

PaO_2 – partial pressure of oxygen in arterial blood

PCT – procalcitonin

PR-AUC – area under the precision-recall curve

ROC – receiver operating characteristic

ROC-AUC – area under the receiver operating characteristic curve

r_rb – rank-biserial correlation

SCCM – Society of Critical Care Medicine

SD – standard deviation

SE RKEB – Semmelweis Egyetem Regionális, Intézményi Tudományos és Kutatásetikai Bizottság

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

TPR – true positive rate

TRIPOD – Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

TRIPOD+AI – Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis + AI extension

VET – viscoelastic testing

WMS – Wilderness Medical Society

1 Introduction

Heat-related illnesses constitute a significant part of emergency medicine practice, a field that is especially influenced by climate change, demographic change, and health-system pressures. Extreme temperatures are a key exposure marker linking climate change to severe health consequences, including death. Their health impact is expected to increase further under climate change and in an ageing population with increasing multimorbidity [1, 2]. An estimation study suggested that in Europe in 2023, there were 47,690 heat-related deaths, and that this number would have been higher in the absence of societal changes [3]. The same research group later published a 2024 estimate based on a harmonised 32-country dataset, reporting approximately 62,775 heat-related deaths; within that analytic framework, the 2024 burden was lower than in 2022 and higher than in 2023 [4]. In temperate climates, thermal exposure occurs not only outdoors but also indoors and within institutions, which increases the need for structured emergency department (ED) assessment of vulnerability to thermal loads. To our knowledge, ED-based data addressing both heat- and cold-related presentations within the same Central European emergency setting remain limited. The vulnerability to temperature-related emergencies in the ED is driven by personal factors, including underlying illnesses, medication use, and housing instability. This transforms the problem from a predictable, outdoor, weather-driven public health issue into a less visible and less predictable one. Because many of these emergencies occur indoors, they may not be fully captured by traditional weather-based prevention or warning systems. Heat stroke and severe hypothermia are life-threatening emergencies. Heat stroke is defined as a rapidly elevated core body temperature accompanied by central nervous system dysfunction and is associated with multi-organ failure due to a systemic inflammatory response, endothelial dysfunction, microvascular failure, and coagulopathy [5, 6]. Management strategies emphasise rapid cooling and the early identification of organ failure [7–10]. Accidental hypothermia, which is defined as a core body temperature below 35 °C, impacts metabolism, respiration, circulation and coagulation. It increases the risk of cardiac arrhythmias and can progress to cardiac arrest [11, 12]. In cases of hypothermic cardiac arrest or persistent shock, international guidance recommends extracorporeal rewarming with extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) [12–14]. However, delays in diagnosis due to overcrowding can make timely

escalation more difficult [15–22]. Machine-learning-based decision-support tools are increasingly explored to ease these pressures, but their real-world performance and governance remain critical considerations [23–25]. These issues highlight the need for practical, triage-level risk assessment, as well as well-managed digital workflow support. Temperature, mental status and a limited set of admission laboratory markers may help to identify risks earlier, reduce diagnostic delays and inform treatment plans during thermal emergencies. This concept is explored in six original studies conducted at a single academic ED. The studies progress from identifying prognostic signals (Pillar 1), to investigating mechanisms in pilot studies (Pillar 2), and finally to developing decision support concepts that could be implemented in practice (Pillar 3).

1.1 Heat stroke in a temperate European emergency department: clinical signal amidst rising heat stress

Heatwaves are becoming more common in Central Europe, with heat-related deaths rising across the continent [3, 4]. Emergency departments (EDs) in temperate climates are now increasingly encountering severe hyperthermia cases that were once considered rare. Classical (non-exertional) heat stroke primarily affects vulnerable populations, particularly older adults with multiple comorbidities, often in indoor settings with limited adaptive capacity [5]. However, current preventive strategies primarily target outdoor temperature exposure, overlooking the broader range of vulnerability factors evident in the increasingly complex caseloads seen in modern EDs. Accordingly, EDs in temperate regions require standardised heat stroke protocols to enable timely cooling and recognition of organ failure, as well as escalation to the intensive care unit (ICU) [7–10].

1.2 Accidental hypothermia: staging limitations and the need for early ED-specific risk stratification

Accidental hypothermia is a complex condition that is difficult to assess and predict in the ED. The Swiss staging system classifies severity based on the presence of shivering and level of consciousness, and a revised version has been developed for use in prehospital and ED settings [26]. However, clinical assessment can be complicated by intoxication, underlying neurological conditions and polypharmacy. When evaluated against hospital and literature cases, the Swiss staging system matched the expected core-

temperature category in only around 61% of instances [27]. The 5A severity scale (Age, Activities of Daily Living, Arrest, Acidemia, Albumin) incorporates laboratory parameters to improve prognostic accuracy [28]. In routine ED practice, core temperature measurement is often delayed or substituted with tympanic readings. Furthermore, hypothermia-specific staging systems have not yet been validated as triage-level tools in urban populations in temperate climates with high rates of housing insecurity and non-thermal causes of altered mental status. Whether a nationally mandated general triage system combined with admission temperature can serve as a feasible prognostic tool at triage level in such populations remains to be seen.

1.3 Workflow constraints, diagnostic delay, and the role of patient-generated data

When EDs become overwhelmed, patients often wait longer to see a physician after their initial check-in. This congestion stems from a mix of rising patient numbers, delays in testing or staffing within the ED, and a lack of available hospital beds for those needing admission [20–22]. During these delays, patients' conditions can deteriorate while vital diagnostic steps stall. This is particularly dangerous for temperature-related emergencies, where every minute spent waiting for cooling or rewarming affects the outcome. A separate but related problem is the delay in diagnostic workup during crowding. Digital questionnaires can collect patient data immediately after triage, potentially enabling shorter intervals from triage to clinician laboratory ordering. While this does not directly accelerate therapeutic interventions such as cooling or rewarming, it may enable earlier risk stratification and thus earlier escalation decisions. When analysed using machine learning (ML), this information can help anticipate which laboratory tests are likely to be ordered, allowing blood sampling to begin before the physician even arrives. Despite this potential, these digital tools often struggle when moved to new environments, and their diagnostic accuracy remains inconsistent. Consequently, maintaining safety requires rigorous oversight, strong governance, and constant performance monitoring [23–25].

1.4 Thermal emergencies as an ED systems and equity challenge

Thermal emergencies represent more than physiological crises; they also challenge the infrastructure. Personal vulnerabilities—such as chronic illness, homelessness, or

intoxication—intersect with systemic constraints like overcrowding and bed shortages to dictate their recovery. In urban areas, accidental hypothermia may also occur indoors [11, 29]. These patients often arrive with an altered mental state, which obscures the severity of their condition and delays life-saving care. This issue is closely linked to social equity, as people experiencing housing insecurity are most likely to be exposed to the cold for long periods of time and to remain undetected for longer. Therefore, any digital tool designed to assist clinicians must be evaluated in terms of equity if it is to be clinically useful. These practical hurdles lead us to the core question of this research: What is the minimum amount of data required under typical ED pressure to accurately guide treatment?

1.5 Hypothermia staging and ED-ready risk models

As many current hypothermia risk models rely on laboratory results unavailable during triage [14], this dissertation explores a more practical approach involving the use of standard triage data combined with admission temperature, with later laboratory refinement reserved for high-risk patients. A key question for clinical translation is whether this streamlined method remains accurate enough to distinguish between patient needs within a busy, real-world ED.

1.6 From risk stratification to workflow-compatible decision support

Predictive models and decision support tools can only deliver results if they can be applied in real emergency situations: they must be fast, interpretable, adaptable to heterogeneous data, and consistent with intervention priorities. Coiera called this the "last mile" problem of medical artificial intelligence (AI), in which organisational, human factors, and safety considerations outweigh algorithmic performance [23]. External validations also suggest that even widely used models lose their discriminatory power and calibration in changing environments and circumstances, as demonstrated by a large-scale, multicentre sepsis prediction model [24]. When treating conditions associated with hypothermia, the outcome depends primarily on early detection and timely escalation. Recent guidelines for the treatment of accidental hypothermia also emphasise the importance of structured triage and clear rewarming strategies, including consideration of extracorporeal life support, but also highlight that the heterogeneity of emergency

practice and limited availability of evidence pose additional challenges [29]. The European Resuscitation Council (ERC) 2025 guidelines revised and refined the algorithms for hypothermic cardiac arrest, integrated the Hypothermia Outcome Prediction after ECLS (HOPE) score, and updated the recommendations for defibrillation and circulatory support [14]. Demographic changes resulting from an ageing society are expected to increase temperature-related mortality in all climate change scenarios examined. This means that emergency departments will have to manage a multimorbid population with heat-related illness more frequently [2, 30]. Paper VI examines whether patient-recorded symptoms can help anticipate which laboratory tests clinicians are likely to order and thereby estimate the potential reduction in the interval from triage to clinician laboratory ordering, while maintaining clinical responsibility and acknowledging the methodological limitations of such tools [25]. This dissertation examines a front-end strategy in which early triage-level objective signals identify risk, a limited early laboratory panel refines that risk in selected patients, and dynamic monitoring or workflow-sensitive digital tools support escalation without replacing clinical judgment. The conceptual framework guiding the dissertation is summarised in Table 1.

Table 1. Conceptual framework linking environmental drivers, patient vulnerability, emergency department processes, and outcomes.

The framework integrates environmental drivers, exposure context, and patient vulnerability with triage, early assessment, treatment, and outcomes at the patient and system levels. Outcomes feed back into a learning loop for protocol and model updating. Created by the candidate for this dissertation. Abbreviations: ED = emergency department, ICU = intensive care unit.

Domain	Components
	UPSTREAM FACTORS
Environmental drivers	Heatwaves; cold spells; contextual factors (urban heat island, housing quality)
Exposure context	Indoor vs. outdoor; duration; co-exposures (alcohol, drugs, immobility)
Patient vulnerability	Age; comorbidity–medication patterns; social vulnerability; baseline functional status
	ED PROCESSES
Triage	Documentation of measurement site (core where feasible, otherwise proxy measurement); symptom questionnaire
Early assessment	Laboratory testing (biomarkers, blood gas); viscoelastic coagulation testing; dynamic monitoring during rewarming
Treatment	Active rewarming / cooling; haemodynamic support; capacity-constraint management
	OUTCOMES
Patient-level	ED death; ICU admission; time to treatment
System-level	Throughput; resource use; workflow acceleration
	LEARNING LOOP
Feedback	Protocol updating; model refinement; prospective validation

2 Objectives

This dissertation aims to develop and evaluate pragmatic risk-stratification concepts for ED patients exposed to thermal stress, and to explore how these concepts can be translated into protocols to accelerate and, where appropriate, escalate workflows.

My objectives were as follows:

- Objective 1 – Early risk stratification in thermal emergencies (Papers I–III): To characterise early clinical and laboratory risk signals in heat stroke (Paper I) and accidental hypothermia (Papers II–III), and to evaluate whether triage-level variables — triage category and admission temperature — can predict early critical outcomes in a temperate-climate ED.
- Objective 2 – Biomarker dynamics and coagulopathy during hypothermic rewarming (Papers IV–V): To assess the dynamics of biomarkers and coagulopathy during rewarming in the early phase of ED care in accidental hypothermia, and whether these trajectories differ between critical and non-critical outcomes.
- Objective 3 – Machine-learning-based workflow acceleration (Paper VI): To develop and internally validate a machine-learning-based model that predicts clinician laboratory orders from patient-reported symptoms collected at triage, and to estimate the potential time savings of an anticipatory workflow before clinician laboratory ordering.

3 Methods

This dissertation comprises six original publications from the Department of Emergency Medicine at Semmelweis University in Budapest. The studies combine retrospective analysis of ED data, prospective pilot sampling, and development of machine learning–based models within a unified framework. The scope ranges from signal identification (Papers I–III) and mechanistic investigation (Papers IV–V) to decision support with a view to practical implementation (Paper VI). All studies complied with ethical and data protection regulations. Where relevant, the publications adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies (Papers II–III) [31] or the adapted STROBE principles for descriptive studies (Paper I). The Hungarian Emergency Triage System (MSTR), which is mandatory in Hungary, is a five-level scale. Patients are classified into emergency categories ranging from Level 1 (immediate) to Level 5 (non-urgent) based on vital signs, symptoms, and risk factors. We extracted the triage classification from the electronic health record (EHR) and used it as an early predictive variable in the study cohorts. The key outcome variables, which are defined consistently throughout the studies, and the included work packages are summarised in Table 2:

- Early critical outcome (hypothermia studies): ED death or ICU admission was used as a proxy for ED-phase severity/escalation, capturing either death during ED care or the need for intensive care-level management.
- ED mortality (heat stroke study; comorbidity study): death occurring in the emergency department.

Table 2. Overview of included studies

Study / Work	Design	Period	Population (n)	Primary endpoint	Status
Heat stroke brief report (Int J Emerg Med 2024)	Retrospective cohort	June–July 2024	8	ED mortality	Published
Hypothermia triage + temperature model (PLoS One 2025)	Retrospective cohort	2020–2024	131	Early critical outcome	Published
Hypothermia comorbidity and staging	Retrospective cohort	March 2021–March 2025	125	ED mortality; clinical staging patterns	Published
Biomarker dynamics during rewarming	Prospective pilot	December 2024–October 2025	18	Early critical outcome	Under review

Study / Work	Design	Period	Population (n)	Primary endpoint	Status
Coagulation pilot: routine + VET	Prospective pilot	December 2024–March 2025	16	Early clinical course; coagulation parameters	Submitted
ML lab order prediction from triage questionnaire	Model development with internal nested cross-validation	October 2023–February 2025	3,925	Prediction of subsequent clinician lab orders; time-to-order	Under review

3.1 Heat stroke study

A retrospective cohort study was conducted at a single academic tertiary emergency department in Budapest. Patients with a body temperature of at least 40 °C between 1 June and 31 July 2024 were identified through screening for International Classification of Diseases, 10th Revision (ICD-10) hyperthermia codes (T67.0–T67.9). A manual chart review was performed to confirm a diagnosis of heat stroke. Heat stroke was defined as documented body temperature ≥40 °C with central nervous system dysfunction (Glasgow Coma Scale (GCS) <15, seizure, or delirium). Early death was defined as death occurring during the index ED visit. The following data were extracted from the EHR: demographics, comorbidities, prehospital factors, admission vital signs, laboratory parameters, clinical management, and ED outcomes. A comparison was made between survivors and non-survivors using Mann–Whitney U tests. Additionally, Cliff's delta was calculated as a non-parametric effect size measure to support the hypothesis test. The emphasis was placed on descriptive clinical patterns and laboratory indicators. Due to the limited sample size, all reported p values are exact two-sided Mann–Whitney U probabilities, and no multiplicity adjustment was applied. No a priori sample-size calculation was performed, as this was a consecutive case series of all eligible patients during the study period. Ethics approval: Semmelweis University Regional and Institutional Review Board (SE RKEB 198/2021).

3.2 Hypothermia triage + temperature model

A retrospective, single-centre study of patients with accidental hypothermia in a temperate-climate emergency department (ED) was conducted. Patients with ICD-10 codes indicating accidental hypothermia (ICD-10 T68) and a tympanic temperature below

35 °C upon arrival were included in the study. Triage category (MSTR) and admission temperature were collected from the electronic health record (EHR). The severity of hypothermia was categorised using measured tympanic temperatures and thresholds from the Swiss staging model and the Wilderness Medical Society (WMS) criteria. An early critical outcome was defined as death in the ED or ICU admission. Discrimination was assessed using the area under the receiver operating characteristic curve (ROC-AUC). The triage category was evaluated both alone and in combination with the admission temperature, with a focus on early, operationally available predictors. Calibration was assessed graphically in the source publication, which also reported calibration metrics including the Brier score, calibration intercept, and calibration slope. Ethics approval: SE RKEB 274/2024.

3.3 Hypothermia comorbidity and staging study

A retrospective cohort study of patients with an ICD-10 code T68 (hypothermia) treated between March 2021 and March 2025 was conducted. The following data were collected from the EHR: demographics, indoor/outdoor discovery context, homelessness status, comorbidities, chronic medications (focusing on polypharmacy and cardiovascular agents), admission laboratory values, and temperature-defined stage categories. The documented Alert–Voice–Pain–Unresponsive (AVPU) value for each patient was tabulated against the temperature-defined stage category to characterise the distribution of consciousness levels across severity categories. Pain and Unresponsive categories were combined owing to the small number of Unresponsive patients (n = 6). Frequent comorbidity–medication combinations were tabulated descriptively using predefined ICD-10 and Anatomical Therapeutic Chemical (ATC) groupings. Given the limited number of ED deaths, exploratory Firth penalized logistic regression was also performed as a sensitivity analysis using prespecified predictor subsets. Consciousness–temperature discordance was defined as a mismatch between the expected consciousness level for a given Swiss staging temperature category and the observed AVPU score. Ethics approval: SE RKEB 274/2024.

3.4 Biomarker dynamics during rewarming

We conducted a prospective pilot study on accidental hypothermia, enrolling 18 patients through convenience sampling without a formal sample-size calculation. We performed paired biomarker measurements in the early stages of rewarming in the ED. Paired sampling was conducted at two pre-defined thermal states. The hypothermic-state draw was obtained shortly after the patient was admitted to the ED (core temperature <35 °C), and a rewarming-state draw was performed at the first documented normothermic assessment (core temperature ≥35 °C). The median time between samples was 3.7 hours (IQR 2.9–5.0). The analyses were conducted during the initial rewarming phase and did not extend beyond the first normothermic time point. Laboratory panels were repeated at admission and, where feasible, upon reaching the first normothermic state (≥35 °C). The parameters examined included blood glucose, haematocrit, complete blood count, high-sensitivity troponin T (hs-TnT), C-reactive protein (CRP), and lactate. We compared the trajectories of biomarkers between cases with critical and non-critical outcomes. Transfer from the emergency department to a general ward or discharge home was classified as a non-critical outcome, whereas a critical outcome was defined as death in the ED or direct admission to the ICU. Patient care followed standard clinical practice; the study protocol did not influence therapeutic decisions. Ethics committee approval number: SE RKEB 274/2024.

3.5 Coagulation pilot with viscoelastic testing

Standard coagulation tests are performed at 37 °C and may therefore mask temperature-dependent coagulopathy in hypothermic patients. To characterise coagulation test profiles obtained during hypothermia and their change during rewarming, a prospective single-centre pilot study assessed routine coagulation tests and viscoelastic testing (VET; ClotPro®, a viscoelastic point-of-care device), measured at the assay temperature of 37 °C, during hypothermia and after rewarming. Sixteen patients were enrolled between December 2024 and March 2025. Patients on anticoagulants were excluded. Extrinsic pathway and ecarin-based assay (ECA) clotting time (CT), clot formation time (CFT), and clot firmness were recorded using ClotPro®. Associations with admission temperature, pH, and early clinical course were explored. Coagulation and VET analyses

were within the approved non-interventional sampling framework. Ethics approval: SE RKEB 274/2024.

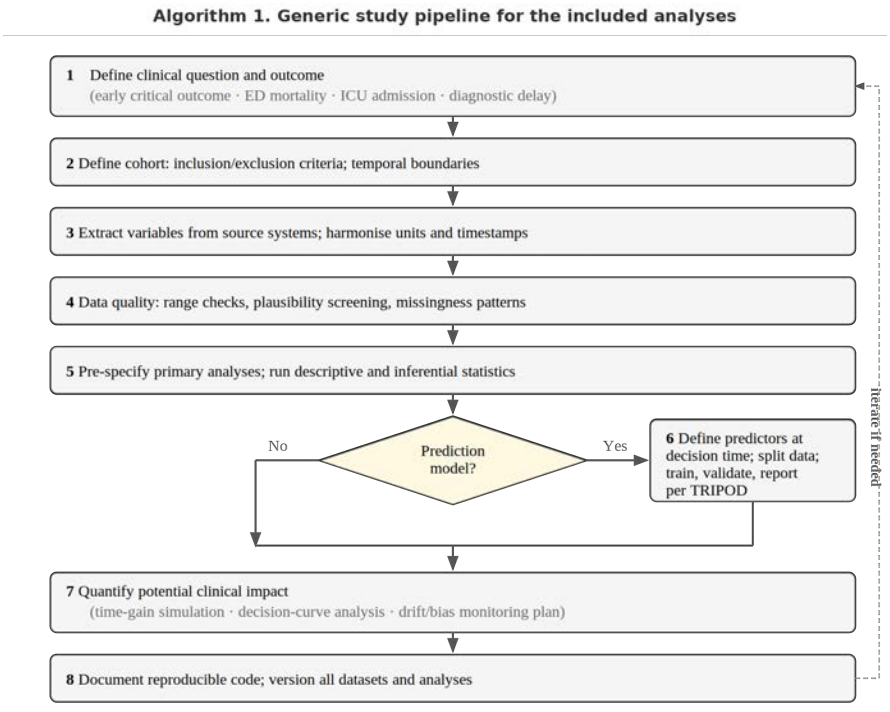
3.6 Machine learning to accelerate laboratory ordering

This study examined whether symptoms reported by patients could predict which laboratory tests a physician was likely to order, and whether such a workflow might shorten the interval from triage to clinician laboratory ordering. The predictive goal of the model was to determine whether specific laboratory tests would be ordered by the attending physician during the index emergency department visit. From October 2023 to February 2025, a non-interventional observational study using prospectively collected questionnaire data and retrospectively linked EHR orders was conducted in a tertiary university emergency department. Adults classified as MSTR categories III–V were asked to complete a digital symptom questionnaire prior to their medical examination (n = 3925). Responses were coded as ordinal or binary variables. Separate models were trained for each laboratory test (C-reactive protein [CRP], D-dimer, aspartate aminotransferase [GOT/AST], N-terminal pro-B-type natriuretic peptide [NT-proBNP], procalcitonin [PCT], and high-sensitivity troponin T [hs-TnT]) to predict whether that test would be ordered within 24 hours. Actual orders extracted from the EHR served as the baseline data. Discrimination was evaluated using ROC-AUC, precision-recall area under the curve (PR-AUC), and recall at a 10% false positive rate, with 10-fold nested cross-validation. The time interval between completing the questionnaire and the physician's order was used to simulate potential time savings. To ensure transparency and reproducibility, reporting was aligned with TRIPOD principles and specifically informed by the TRIPOD+AI framework [32, 33]. Ethical approval was granted by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council, case number: BM/18039-3/2023.

3.7 Statistical approach and model evaluation

Even though the individual studies in this dissertation differ in design and sample size, the predictive analyses follow a consistent analytical approach. Where applicable, they prioritise predictors available at triage and systematically evaluate model performance. The statistical methods used in each study were adapted to the specific design and sample

size. Continuous variables were characterised by either the mean and standard deviation (SD) or the median and interquartile range (IQR), depending on their distribution. Nonparametric tests were used to compare small samples. To complement null-hypothesis testing, effect sizes were also reported: Cliff's delta for the Mann–Whitney U test (Papers I, IV, and V), rank-biserial correlation for paired non-parametric analyses (Papers IV–V), and Cohen's d_z for paired t-tests. Where sample size permitted, logistic regression was used for multivariable prediction analyses; smaller studies remained descriptive or exploratory. We quantified discriminatory ability using ROC-AUC and reported 95% confidence intervals (CI). However, for low-prevalence outcomes such as rarely requested laboratory tests, ROC-AUC can be misleading. Therefore, we also calculated PR-AUC, which more accurately reflects the predictive performance of the positive class. In the machine learning study, the models were developed and evaluated using 10-fold nested cross-validation. Hyperparameter optimisation was restricted to the inner training folds, so performance estimates from the outer test folds were less prone to optimism. In Paper III, we analysed patterns of comorbidity and medication co-occurrence. Figure 1 illustrates the steps involved in the common analysis process across the studies.



Created for this dissertation.

Figure 1. Generic study pipeline for the included analyses. Source: Own figure (created by the candidate).

Flowchart illustrating the shared analytic pipeline across the six studies: data source identification → cohort definition → variable extraction → statistical analysis → interpretation → integrated synthesis within the three-pillar framework.

4 Results

This chapter presents the main findings of the included studies (Papers I–VI). Results from published studies are reported as they appear in the peer-reviewed articles. For under review or submitted manuscripts and pilot studies (Papers IV–VI; Section 9), the findings reflect the manuscript versions available at the time of dissertation submission.

4.1 Heat stroke: early death and laboratory signals

Between 1 June and 31 July 2024, 22 emergency patients were diagnosed with hyperthermia according to the ICD-10 classification system (codes T67.0–T67.9). Following a manual review of the medical records, eight patients who met the study case definition and had a documented body temperature of at least 40 °C were identified. Three of these patients (37.5%) died in the emergency department (Table 3). Non-survivors were numerically younger (median 47 vs. 69 years, $p = 0.393$) and had significantly lower pH (7.07 vs. 7.40), higher potassium levels (7.3 vs. 3.2 mmol/L), higher lactate levels (10.9 vs. 3.5 mmol/L) and higher $PaCO_2$ values (57.2 vs. 28 mmHg) (all $p = 0.036$). Ionised calcium was higher in non-survivors (1.19 vs. 0.97 mmol/L; $p = 0.036$). The core temperature measured at admission was lower in non-survivors (40.6 vs 42.2 °C; $p = 0.294$). Because of the very small sample size, the exact two-sided Mann–Whitney U test could yield only a limited set of discrete p values; this explains why several comparisons share the same p value (0.036). Figure 2 shows these clinical events in the context of the broader environmental conditions during the study period, including recurring extreme heatwaves (daily maximum temperature >35 °C) in summer and prolonged periods below freezing in winter. Figure 3 illustrates the precise temporal distribution of emergency admissions due to heat stroke during the study period.

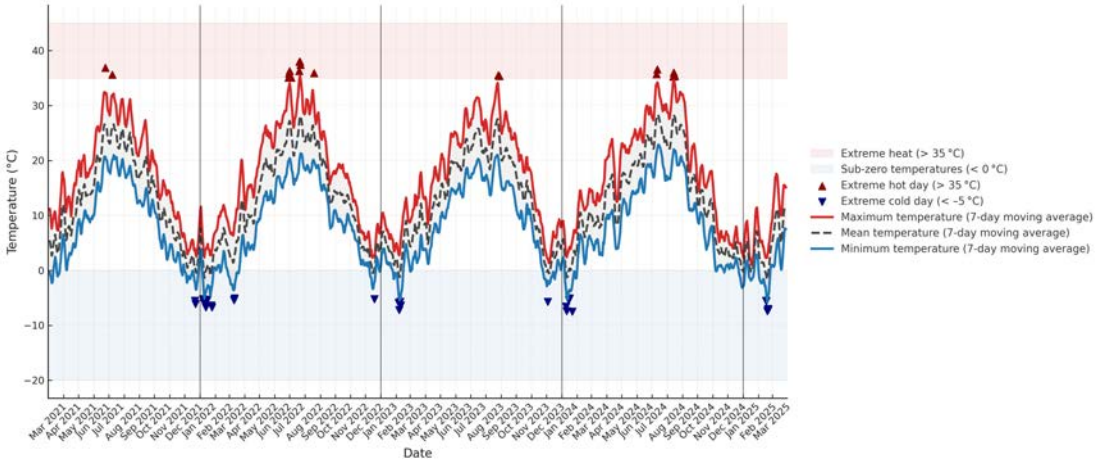


Figure 2. Ambient temperature extremes in Budapest during the study period (March 2021–March 2025). Source: Own figure (created by the candidate).

Seven-day moving averages of daily maximum (red), mean (dashed grey), and minimum (blue) ambient temperatures. The pink shaded zone marks extreme heat (>35 °C) and the light blue zone marks sub-zero temperatures (<0 °C). Red upward triangles indicate extreme hot days (daily maximum >35 °C); blue downward triangles indicate extreme cold days (daily minimum < −5 °C). Vertical grey lines denote calendar-year boundaries.

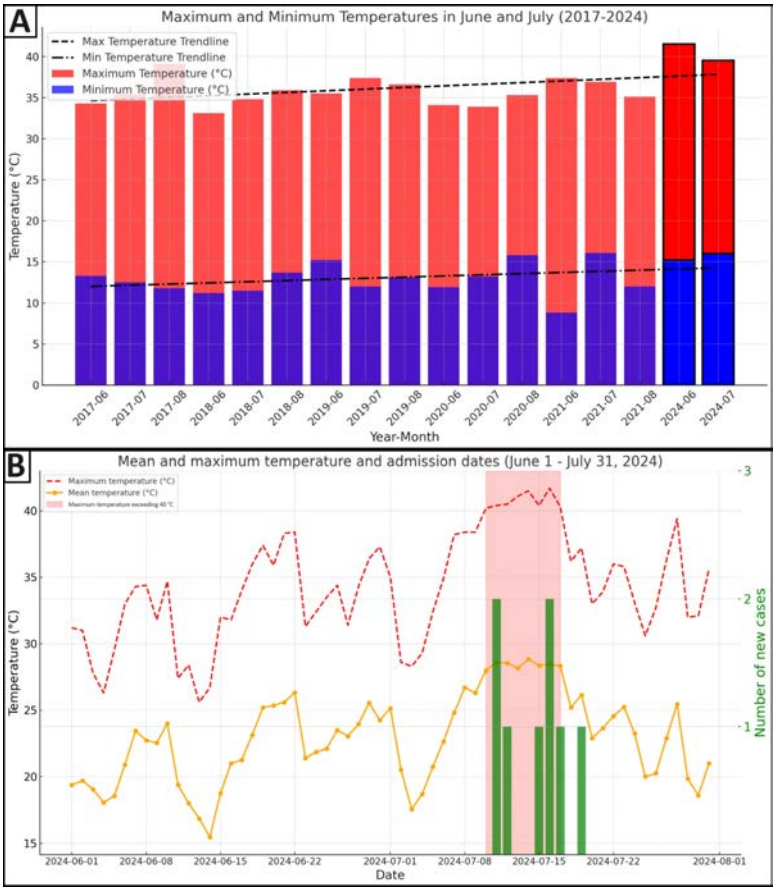


Figure 3. Temperature extremes and heat stroke-related ED admissions (June–July). Source: Own figure (created by the candidate; data from Paper I [10]).

Panel A—monthly maximum and minimum temperatures for June and July (2017–2024). Panel B—daily maximum and mean temperature overlaid with daily heat-stroke admissions between 1 June and 31 July 2024. ED admission data derive from Paper I. Created by the candidate [10].

Table 3. Paper I—comparison of clinical and laboratory characteristics between patients who died in the ED and those who survived the ED stay.

Age is reported as the median; values in parentheses denote IQR width (not IQR bounds), mirroring the source publication.

Parameter	Died in ED (n=3)	Survived ED stay (n=5)	p value
Age (years)	47 (IQR 17.5)	69 (IQR 10)	0.393
Sex (male), n (%)	3 (100%)	3 (60%)	0.673
Core body temperature (°C)	40.6	42.2	0.294
pH	7.07	7.40	**0.036**
PaO_2 (mmHg)	121	200	0.393
$PaCO_2$ (mmHg)	57.2	28	**0.036**
HCO_3^- (mmol/L)	16.4	19	0.571
Base excess (mmol/L)	-13.8	-6	0.071
Na^+ (mmol/L)	131	126	0.571
K^+ (mmol/L)	7.3	3.2	**0.036**
Ionised Ca^{2+} (mmol/L)	1.19	0.97	**0.036**
Lactate (mmol/L)	10.9	3.5	**0.036**

4.2 Accidental hypothermia: triage category and admission temperature predict early critical outcomes

In our cohort of 131 patients with accidental hypothermia (median age: 67 years; 67.2% male), the median tympanic temperature upon admission was 29.3 °C. Of these patients, 35.9% arrived with severe hypothermia (defined as a temperature below 28 °C). An early critical outcome occurred in 33.6% of cases (44 out of 131). Of these, 16 patients required admission to the intensive care unit and 28 died during emergency care. Figure 4 shows the seasonal distribution of temperature-threshold-defined severity categories corresponding to the Swiss stage ranges, alongside the evolution of ambient temperature. Table 4 summarises the baseline patient characteristics. Triage category alone showed moderate discriminatory power in predicting early critical outcomes (ROC-AUC: 0.683; 95% CI: 0.598–0.767), which improved when admission body temperature was included (ROC-AUC: 0.740; 95% CI: 0.644–0.829). The discrimination indices of the models are

presented in Table 5, the ROC curves are shown in Figure 5 and the calibration results are displayed in Figure 6.

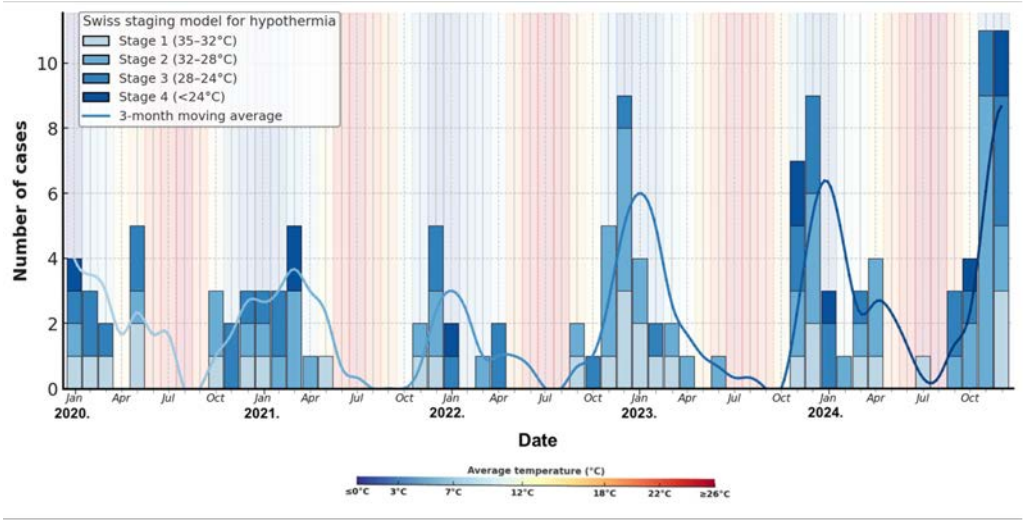


Figure 4. Monthly distribution of accidental hypothermia presentations by temperature-threshold-defined stage categories based on admission tympanic temperature (2020–2024). Source: Own figure (created by the candidate; data from Papers II [34] and III [35]).

Stacked bar chart of monthly hypothermia case counts stratified by temperature-threshold categories corresponding to Swiss stage ranges: Stage I equivalent (≥32.0 to <35.0 °C, lightest blue), Stage II equivalent (≥28.0 to <32.0 °C), Stage III equivalent (≥24.0 to <28.0 °C), and Stage IV equivalent (<24.0 °C, darkest blue). The blue curve represents the 3-month moving average of total monthly cases. The background colour gradient encodes mean monthly ambient temperature (dark blue ≤0 °C through yellow to red ≥26 °C), illustrating the seasonal concentration of presentations during cold months.

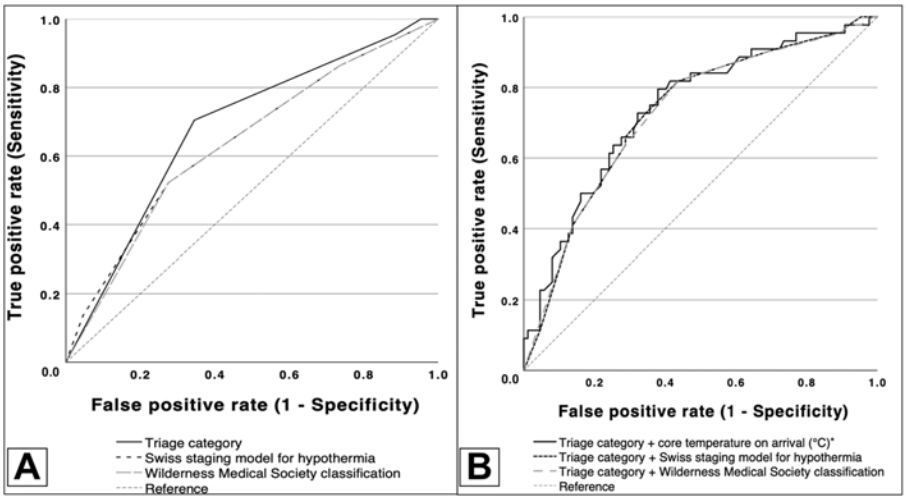


Figure 5. ROC curves for early critical outcome prediction in accidental hypothermia (Paper II). Source: Own figure (created by the candidate; Paper II [34]).

Receiver operating characteristic (ROC) curves with AUC (95% CI) for prediction of early critical outcome (ED death and/or ICU admission) using: (i) Hungarian Emergency Triage System (MSTR) triage category alone, (ii) admission tympanic temperature alone, (iii) traditional Swiss staging, (iv) Wilderness Medical Society (WMS) staging, and (v) the combined model (triage category + admission tympanic temperature) [34].

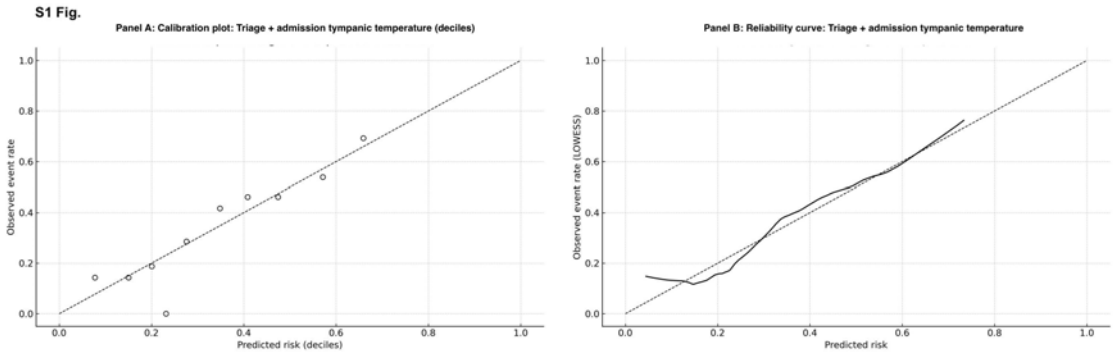


Figure 6. Calibration of the combined hypothermia risk model (Paper II). Source: Own figure (reproduced from Supporting information S1 Fig of Paper II [34]).

Calibration plot (observed vs. predicted risk) for the combined model (triage category + admission tympanic temperature). Reproduced from Supporting information S1 Fig of Paper II [34].

Table 4. Paper II—baseline characteristics and outcomes of the accidental hypothermia cohort.

Characteristic / outcome	Overall (n=131)
Age, years (median, IQR)	67.0 (59.0–75.0)
Male sex, n (%)	88 (67.2%)
Tympanic temperature at arrival, °C (median, IQR)	29.3 (26.1–31.4)
Severe hypothermia (<28 °C), n (%)	47 (35.9%)
ED length of stay, hours (median, IQR)	13.7 (9.5–18.9)
ICU admission, n (%)	16 (12.2%)
ED death, n (%)	28 (21.4%)
Early critical outcome (ED death or ICU admission), n (%)	44 (33.6%)

Table 5. Paper II—model performance for predicting early critical outcomes in accidental hypothermia.

Predictor/model	AUC (95% CI)	Notes
MSTR triage category (alone)	0.683 (0.598–0.767)	ED triage category (MSTR) at presentation
Admission tympanic temperature (alone)	0.666 (0.566–0.764)	Continuous; tympanic measurement at ED arrival

Predictor/model	AUC (95% CI)	Notes
MSTR triage + admission tympanic temperature	0.740 (0.644–0.829)	Multivariable logistic regression; triage category + continuous tympanic temperature
Traditional Swiss staging (alone)	0.644 (0.545–0.736)	Temperature-threshold-defined categories corresponding to Swiss stage ranges
Wilderness Medical Society (WMS) staging (alone)	0.637 (0.536–0.730)	Temperature-threshold-defined WMS classification

4.3 Accidental hypothermia: comorbidity and medication prevalence patterns and consciousness–temperature discordance

Paper III [35] included 125 patients with accidental hypothermia treated in a large academic ED between March 2021 and March 2025. This cohort partially overlaps with the one in Paper II (n = 131; 2020–2024); the differences stem from the later start and end dates, as well as additional selection criteria regarding the completeness of data on comorbidities and medication use. The emergency department mortality rate was 18.4% (23/125). Nearly half of the patients (55/125; 44.0%) had no registered residence. Table 6 summarises baseline demographic and housing characteristics by stage based on temperature thresholds. Altered mental status was the most common presenting complaint, and patients were found indoors as often as outdoors. The level of consciousness often differed from the severity determined by temperature: 30.0% of Stage III patients and 18.2% of Stage IV patients were alert. In contrast, 34.6% of Stage I patients responded only to pain or were unresponsive. Figure 7 shows the prevalence of specific comorbidities, chronically used medication groups, and acute alcohol intoxication by severity category. In all stages, alcoholism and cardiovascular diseases were the most common comorbidities, while among medications, beta-blockers and benzodiazepines were most frequently recorded. Acute alcohol intoxication occurred in all severity categories, and its prevalence did not increase significantly with increasing severity (from 26.9% in Stage I to 36.4% in Stage IV; $p = 0.741$). The associations between comorbidity-medication patterns and ED mortality did not reach statistical significance. According to exploratory analyses performed with Firth correction, each 1 °C increase in tympanic temperature was associated with lower odds of ED mortality (odds ratio [OR] 0.83; 95% CI 0.72–0.95; $p = 0.005$), while no single comorbidity or drug class proved to be a robust predictor.

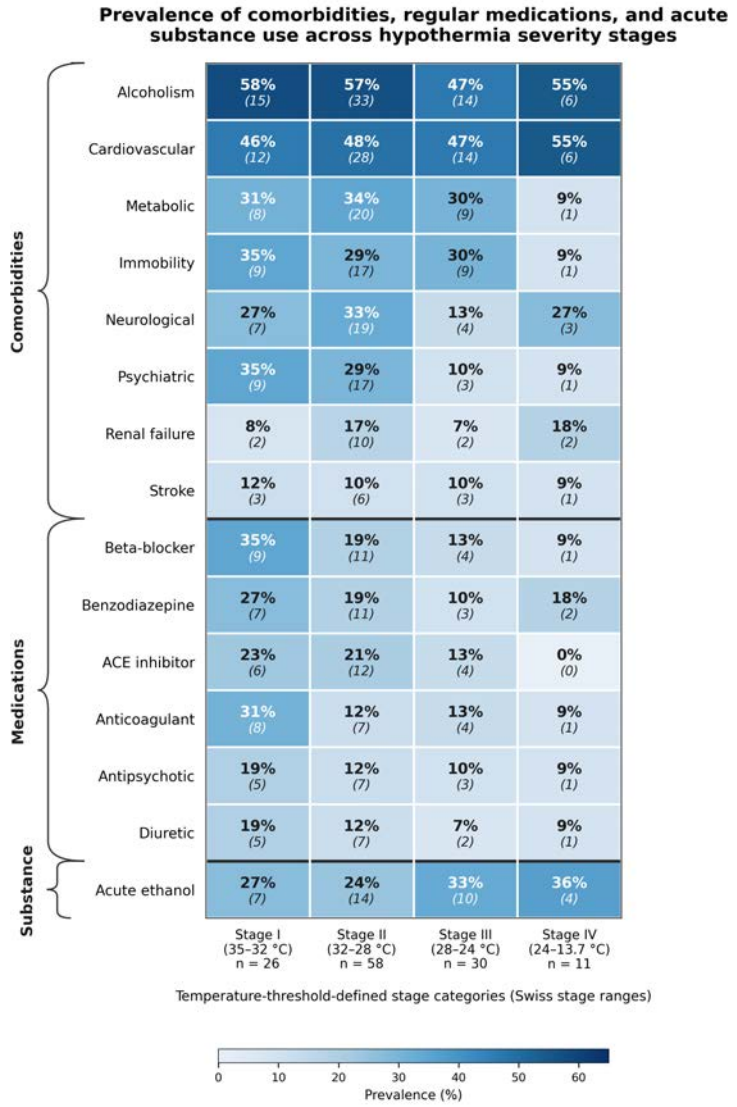


Figure 7. Prevalence of comorbidities, regular medications, and acute substance use across temperature-threshold-defined severity categories corresponding to Swiss stage ranges (Paper III). Source: Own figure (created by the candidate; Paper III [35]).

Heatmap showing the prevalence (%) and absolute count (n) of individual comorbidities, regular medication classes, and acute ethanol intoxication across temperature-defined stage categories (Stage I: 35–32 °C, n = 26; Stage II: 32–28 °C, n = 58; Stage III: 28–24 °C, n = 30; Stage IV: <24 °C, n = 11). Categories were assigned by measured tympanic temperature according to the original Swiss System thresholds (Paper III).

Table 6. Demographic and residence characteristics by temperature-threshold-defined severity categories corresponding to Swiss stage ranges (Paper III).

Characteristic	Overall (n=125)	Stage I (n=26)	Stage II (n=58)	Stage III (n=30)	Stage IV (n=11)
Age, mean ± SD (years)	66.2 ± 13.2	68.2 ± 12.4	67.5 ± 13.2	60.6 ± 13.9	69.9 ± 9.7
Male sex, n (%)	86 (68.8%)	19 (73.1%)	39 (67.2%)	18 (60.0%)	10 (90.9%)
Female sex, n (%)	39 (31.2%)	7 (26.9%)	19 (32.8%)	12 (40.0%)	1 (9.1%)
Residential address: Capital city, n (%)	38 (30.4%)	9 (34.6%)	15 (25.9%)	9 (30.0%)	5 (45.5%)
Residential address: City, n (%)	31 (24.8%)	6 (23.1%)	18 (31.0%)	7 (23.3%)	0 (0.0%)
Residential address: Village, n (%)	1 (0.8%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
Residential address: Homeless, n (%)	55 (44.0%)	11 (42.3%)	24 (41.4%)	14 (46.7%)	6 (54.5%)

4.4 Biomarker dynamics during rewarming in accidental hypothermia: exploratory pilot findings

Our single-centre pilot study (Paper IV, under review) included 18 adult patients with accidental hypothermia (tympanic temperature <35 °C measured during triage, core temperature <35 °C measured as part of routine care). In these patients, paired sampling and status assessment were performed during the early rewarming phase. Among the 18 patients, 8 cases resulted in an early critical outcome (defined in Section 3.2 as death in the ED or ICU admission). The median age was 68.0 years (IQR 56.2–75.5); 10 patients were male. Critical outcome was associated with altered consciousness noted at admission, while baseline body temperature was descriptively lower in the critical group. The median interval between the paired hypothermic and rewarmed-state assessments was 3.7 hours (IQR 2.9–5.0). Of the 18 patients included, 12 reached ≥35 °C during monitored in-hospital rewarming. Of the eight patients with critical outcomes, five failed to achieve normothermia within the observation window, compared with one of the ten patients with non-critical outcomes. Among those who reached ≥35 °C, the median time to the first normothermic assessment was 3.2 hours (IQR 2.4–4.6); patients with critical outcomes had longer times to first normothermic assessment (median 5.1 hours; IQR 3.9–5.5) than patients with non-critical outcomes (median 3.0 hours; IQR 2.0–4.2), although this difference did not reach statistical significance (Mann–Whitney U = 22.0; p = 0.15; Cliff's δ = 0.63). Core temperature on admission was descriptively lower in the critical group (median 28.0 °C; IQR 25.1–29.9 vs. 32.0 °C; IQR 30.3–33.4; uncorrected p = 0.033; Cliff's δ = −0.61), but the distributions overlapped, and this difference did not remain after Benjamini–Hochberg correction. The hourly rate of warming did not differ

between the groups (critical: median 1.02 °C/h; non-critical: 0.81 °C/h; p = 0.32). During rewarming, several biomarkers showed exploratory paired changes until the first normothermic state (≥35 °C) was reached (Table 7): blood glucose, haematocrit, red blood cell count, lymphocyte count, and lymphocyte percentage decreased, while hs-TnT and CRP levels increased. The differences in warming-related changes (Δ) between groups are illustrated in Figure 8. Many of the Δ differences between groups were more pronounced in the critical outcome group. At the first normothermic assessment (≥35 °C), we observed a neutrophil predominance and lymphopenia in the critical outcome group; the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in the critical group (median 18.52; IQR 15.83–33.50) than in the non-critical group (median 2.22; IQR 1.91–7.81; Mann–Whitney U-test, Cliff's δ = 0.92; p = 0.016). Several of these signals warrant caution. The small mean corpuscular haemoglobin change most likely reflects analytical variability rather than haemodilution, and the lower alkaline phosphatase and alanine aminotransferase values are consistent with volume resuscitation and haemodilution rather than hepatocellular injury. The high-sensitivity troponin T and NT-proBNP changes cannot be separated from resuscitation intensity and illness severity. These biomarker signals are therefore exploratory and hypothesis-generating.

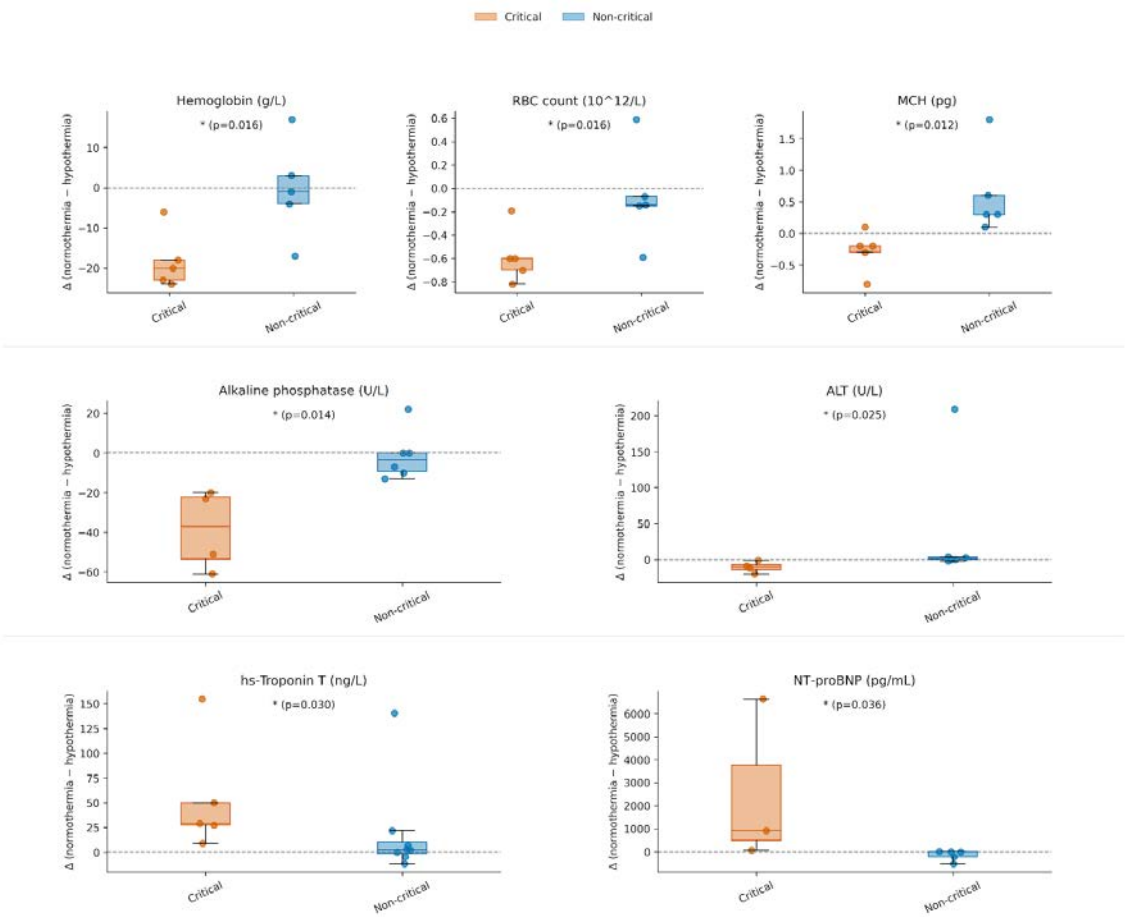


Figure 8. Rewarming-related changes in laboratory parameters by outcome group (Paper IV). Source: Own figure (created by the candidate; Paper IV).

Box-and-swarm plots of rewarming-related delta values (rewarmed-state value [≥35 °C] minus hypothermic-state value) by outcome group. Variables shown are those with significant between-group differences in delta during early rewarming: haemoglobin, red blood cell count, mean corpuscular haemoglobin, alkaline phosphatase, alanine aminotransferase, high-sensitivity troponin T, and NT-proBNP. These are between-group delta differences, not the complete set of significant within-patient paired changes. Orange = critical outcome; blue = non-critical outcome.

Table 7. Significant paired changes during early rewarming from hypothermia to rewarmed state (≥35 °C) (Paper IV).

Values are reported as mean ± SD or median (IQR). The table reports within-patient paired changes (hypothermic to rewarmed state) significant at $p < 0.05$ across patients with paired data; Figure 8 displays between-group differences in delta values (critical vs.

non-critical), which represent a separate comparison layer. These two analyses address different questions, and their variable sets therefore do not overlap completely.

Variable	n	Hypothermic state	Rewarmed state	Test	Effect size metric	Effect size	p value
Glucose (mmol/L)	8	7.15 (5.95–21.05)	5.15 (4.15–14.15)	Wilcoxon	Rank-biserial r	-1.00	0.008
Lymphocyte count (G/L)	10	1.37 ± 0.92	1.13 ± 0.83	Paired t-test	Cohen's d_z	-0.99	0.012
Haematocrit (L/L)	10	0.36 ± 0.08	0.32 ± 0.07	Paired t-test	Cohen's d_z	-0.92	0.017
hs-TnT (ng/L)	13	24.50 (15.40–66.10)	45.80 (20.40–93.50)	Wilcoxon	Rank-biserial r	0.67	0.019
C-reactive protein (mg/L)	10	19.95 (5.22–38.20)	30.80 (6.93–53.53)	Wilcoxon	Rank-biserial r	0.80	0.020
Red blood cell count (×10^12/L)	10	4.02 ± 0.86	3.69 ± 0.79	Paired t-test	Cohen's d_z	-0.78	0.036
Lymphocyte proportion (%)	10	18.20 ± 15.57	13.79 ± 13.37	Paired t-test	Cohen's d_z	-0.74	0.045

4.5 Coagulation changes in accidental hypothermia: routine tests and viscoelastic pilot study

We enrolled 16 patients in our VET pilot study, 8 of whom had an early critical outcome (defined in Section 3.2 as death in the ED or ICU admission). VET results measured during hypothermia were available for 14 patients (7 with critical outcomes and 7 with non-critical outcomes). The timing of baseline VET sampling was similar across the outcome groups: the hypothermic sample was collected at a median time of 18.5 minutes after arrival in the critical group and 20.0 minutes in the non-critical group. Among patients with paired rewarming samples, the interval between the hypothermic and rewarming VET samples was descriptively longer in critical cases (median 321 minutes vs. 209.5 minutes). Core temperature at admission was significantly lower in patients in the critical outcome group (median 27.9 °C; IQR 25.1–29.9) than in the non-critical group (median 32.0 °C; IQR 30.8–33.0; Mann–Whitney U = 12.5; p = 0.046; Cliff's δ = −0.61). Of the 16 patients included, 11 achieved normothermia (≥35 °C) during monitored rewarming. Notably, only 3 of the 8 patients in the critical outcome group reached this threshold, compared with all 8 non-critical patients (Fisher's exact test, p = 0.026). Among those who reached ≥35 °C, the descriptive time to the first normothermic assessment was longer in the critical group (median 5.1 hours; IQR 3.9–5.5 vs. 3.2 hours; IQR 2.4–4.3; p = 0.19; Cliff's δ = 0.58), while the overall rate of warming did not differ between groups

(critical: 1.02 °C/h; non-critical: 0.81 °C/h; p = 0.44). Core temperature measured at the time of VET sampling in the warmed state was similar in all patients (range: 35.0–35.4 °C). In an exploratory, uncorrected comparison of hypothermic samples, the Ecarin-based clotting time (ECA-CT) and clot formation time (ECA-CFT) were longer in the critical outcome group than in the non-critical group (ECA-CT: 112.0 [92.5–119.0] vs. 65.0 [59.0–94.5]; ECA-CFT: 100.0 [92.5–127.5] vs. 70.0 [65.0–80.0]) (Table 8). The Hodges–Lehmann differences were 31.0 s (95% CI 4.0–57.0) for ECA-CT and 30.0 s (95% CI 10.0–70.0) for ECA-CFT. The difference in extrinsic clotting time (EX-CT) did not reach significance. In paired exploratory analyses (n = 10, depending on assay completeness), ecarin-based times shortened after rewarming, and the magnitude of change was greater in the critical outcome group (Hodges–Lehmann Δ between groups: −39.5 s [from −66.0 to −8.0] for ECA-CT; −22.5 s [from −110.0 to −5.0] for ECA-CFT) (Table 8). Changes in extrinsic clotting time were smaller and did not differ significantly between groups. In exploratory correlation analyses (n = 14), admission temperature and pH showed an inverse correlation with ECA-CT. Paired, within-subject changes during warming are illustrated in Figure 9.

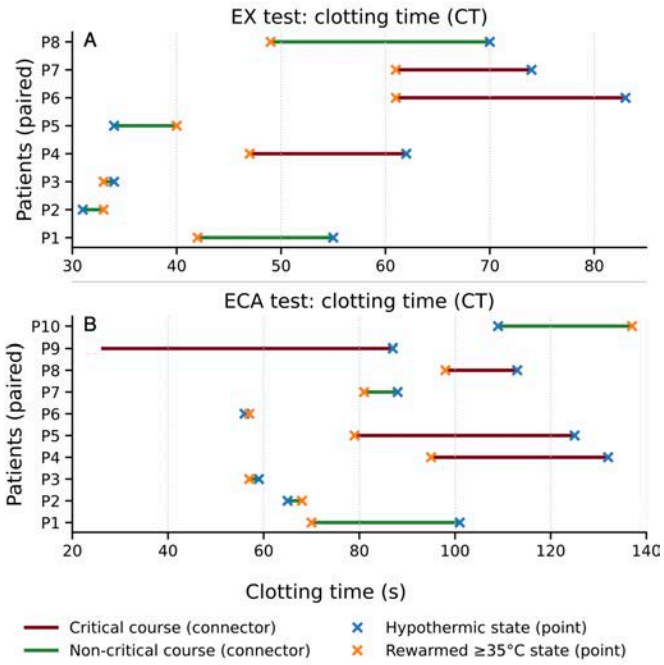


Figure 9. Paired viscoelastic clotting time changes during initial ED rewarming (Paper V). Source: Own figure (created by the candidate; Paper V).

Paired dumbbell plots (hypothermic-state vs. rewarmed-state, ≥35 °C) for EX-CT (Panel A, n = 8 paired) and ECA-CT (Panel B, n = 10 paired), measured at 37 °C. Individual

patient trajectories are shown, with dark red connectors for critical-course and green connectors for non-critical-course patients. Blue crosses = hypothermic-state values; orange crosses = rewarmed-state values (Paper V).

Table 8. Viscoelastic clot initiation and formation parameters (VET at 37 °C): hypothermic-state values and paired changes after rewarming (Paper V).

Values are median [IQR]. Δ = rewarmed-state value − hypothermic-state value. Within-group paired p: Wilcoxon signed-rank test. Between-group p: Mann–Whitney U test. HL = Hodges–Lehmann estimator of location shift; r_rb = rank-biserial correlation. Patients on direct oral anticoagulants and other anticoagulants were excluded. Bold p values indicate $p < 0.05$.

Panel A. Hypothermic-state values						
Parameter	**Overall** *median [IQR]*	**Critical** *median [IQR]*	**Non-critical** *median [IQR]*	***p value***	**HL** *[95% CI]*	***r*** *rb*
EX-CT (s)	60.0 [41.5–73.0] *(n = 14)*	62.0 [60.0–78.5] *(n = 7)*	37.0 [34.0–62.5] *(n = 7)*	0.090	25.0 [−10.0; 43.0]	0.55
ECA-CT (s)	92.5 [70.5–111.2] *(n = 14)*	112.0 [92.5–119.0] *(n = 7)*	65.0 [59.0–94.5] *(n = 7)*	**0.025**	31.0 [4.0; 57.0]	0.71
ECA-CFT (s)	87.5 [71.2–98.8] *(n = 14)*	100.0 [92.5–127.5] *(n = 7)*	70.0 [65.0–80.0] *(n = 7)*	**0.003**	30.0 [10.0; 70.0]	0.90
Panel B. Paired Δ after rewarming (rewarmed − hypothermic)						
Parameter	—	**Critical Δ** *median (n)*	**Non-critical Δ** *median (n)*	***p value***	**HL** *[95% CI]*	***r*** *rb*
EX-CT (s)	—	−15.0 *(n = 3; p = 0.250)*	−1.0 *(n = 5; p = 0.625)*	0.179	−14.0 [−28.0; 8.0]	−0.67
ECA-CT (s)	—	−41.5 *(n = 4; p = 0.125)*	−0.5 *(n = 6; p = 0.844)*	**0.019**	−39.5 [−66.0; −8.0]	−0.92
ECA-CFT (s)	—	−17.5 *(n = 4; p = 0.250)*	5.0 *(n = 6; p = 0.250)*	**0.019**	−22.5 [−110.0; −5.0]	−0.88

4.6 Machine learning to accelerate laboratory ordering from triage questionnaire data

This study (Paper VI, under review) examined whether the symptoms reported by adult patients in MSTR categories III–V during triage could predict the laboratory tests subsequently ordered by the attending physician and whether this would allow estimation of the potential reduction in the time interval between triage and the first medical laboratory order. Random forest models trained on structured symptom data achieved moderate to strong discriminatory power for several common laboratory tests (ROC-AUC 0.74–0.88). The highest ROC-AUC value was measured for GOT/AST (0.88), while the lowest was for CRP (0.74). CRP also showed the highest PR-AUC (0.95), which was associated with the highest ordering prevalence (90%). The median time savings potential ranged from 1 hour 12 minutes (for PCT) to 1 hour 53 minutes (for D-dimer), with 95th percentile values ranging from 4 hours 19 minutes to 6 hours 28 minutes. The performance metrics of the models are summarised in Table 9 and Figure 10, and the estimated time savings are summarised in Table 10.

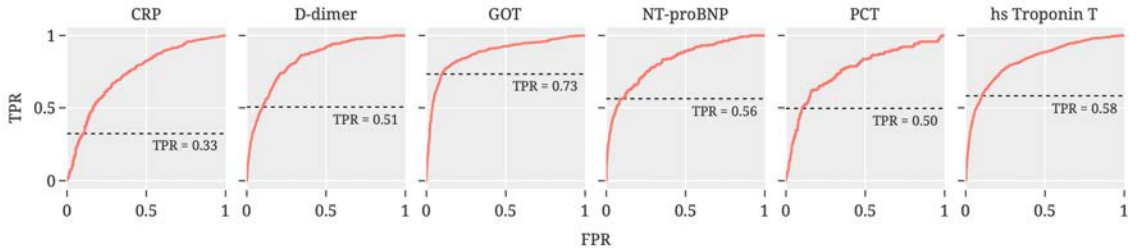


Figure 10. Model discrimination for lab-order prediction from triage symptoms (Paper VI). Source: Own figure (created by the candidate; Paper VI).

Receiver operating characteristic curves for each target laboratory assay (CRP, D-dimer, GOT/AST, NT-proBNP, PCT, hs-TnT). Dashed horizontal lines indicate the true positive rate (TPR) at the prespecified operating point of 10% false positive rate (FPR). AUC values are reported in Table 9 (Paper VI).

Table 9. Paper VI—model performance for anticipatory laboratory ordering using patient-reported symptoms at triage.

Lab assay	Received test (% of patients)	Samples used (n)	ROC-AUC	PR-AUC
C-reactive protein (CRP)	90%	3098	0.74	0.95
D-dimer	12%	3772	0.83	0.44
Aspartate aminotransferase (GOT/AST)	35%	3192	0.88	0.81
NT-proBNP	6%	3857	0.83	0.39

Lab assay	Received test (% of patients)	Samples used (n)	ROC-AUC	PR-AUC
Procalcitonin (PCT)	4%	3635	0.76	0.15
High-sensitivity troponin T (hs-TnT)	24%	3624	0.83	0.65

Table 10. Paper VI—triage symptom questionnaire duration and potential time saved (anticipatory sampling to first order) for each laboratory assay.

Assay-specific sample counts differ because model development used test-specific eligible subsets after predefined preprocessing and exclusion steps; therefore, the denominator is not identical across laboratory targets.

Lab assay	Symptom questionnaire duration median (95th percentile)	Potential time saved to first order median (95th percentile)
C-reactive protein (CRP)	3 min (9 min)	1 h 19 min (4 h 19 min)
D-dimer	3 min (10 min)	1 h 53 min (6 h 28 min)
Aspartate aminotransferase (GOT/AST)	3 min (9 min)	1 h 18 min (4 h 30 min)
NT-proBNP	4 min (10 min)	1 h 22 min (4 h 38 min)
Procalcitonin (PCT)	4 min (12 min)	1 h 12 min (4 h 19 min)
High-sensitivity troponin T (hs-TnT)	4 min (10 min)	1 h 22 min (4 h 39 min)

5 Discussion

The six studies range from clinical descriptive analyses to model building based on machine learning. The findings on heat stroke and hypothermia—despite the two temperature extremes—ultimately point to the same fundamental principle: objective parameters available at emergency admission, such as blood gas values, electrolytes, triage category, and body temperature—can provide meaningful risk indicators even in the earliest stages of care, despite confounding factors such as intoxication-related impairment of consciousness complicating the picture [10, 34]. The consciousness–temperature discrepancy reported in Paper III highlights the limitations of consciousness-level-based staging in heterogeneous urban populations and supports the use of triage systems as a pragmatic prognostic framework supplemented with syndrome-specific modifiers in thermal emergencies. It is important to emphasise that clinical decision-making continues to play a central role, and the proposed framework is not intended to replace bedside medical judgment, but rather to provide low-resource, orienting reference points. Prospective pilot studies take this line of thinking further by extending the concept from static admission predictors to dynamic monitoring. The paired biomarker and viscoelastic changes observed during early rewarming differed between the outcome groups: the elevated NLR observed in patients with critical outcomes indicated a neutrophil-dominant inflammatory response, while the fifth report – in patients not receiving anticoagulants – showed prolonged ecarin-based clotting times, which is compatible with the broader rationale for early viscoelastic assessment in bleeding-risk states [36–38]. It should be noted that these observations are exploratory in nature. However, they support the plausibility of trajectory-based monitoring during the physiologically unstable early warming period. The machine learning thread addresses a specific operational bottleneck: symptoms reported during triage predicted selected laboratory orders with moderate-to-strong internal discrimination, and simulation suggested shorter intervals from triage to clinician ordering. However, it is important to acknowledge the limitations of the approach: predicting a clinician's orders is not the same as predicting a patient's actual needs, and the downstream impact on outcomes remains unproven. The process involves three stages: triage-based early risk stratification, targeted early laboratory evaluation, and dynamic monitoring during cooling or warming.

As the retrospective and prospective cohorts partially overlap, this convergence of results should be interpreted as internal coherence rather than independent validation.

5.1 Novel contributions

This dissertation makes five interconnected contributions to emergency medicine and ED decision support.

1. At its core is Paper II, which shows that, in cases of accidental hypothermia, combining the nationally mandated MSTR triage category with admission tympanic temperature yielded higher point-estimate discrimination for early critical outcomes than isolated hypothermia staging systems in this single-centre cohort. Importantly, this approach uses only the variables available during the initial patient assessment, providing a pragmatic, low-burden risk indicator that aligns seamlessly with standard ED triage procedures.

The accompanying studies serve to contextualise and extend this primary finding.

2. Paper I addresses the hyperthermic end of the spectrum and indicates that heat stroke remains a clinically relevant reality even in temperate Central European settings, where arterial blood gas (ABG) and electrolyte derangement may flag the need for rapid escalation.
3. Paper III further refines the diagnostic framework by suggesting that, in socially vulnerable urban populations, objective temperature measurement should be prioritised over relying on mental status-based staging alone.
4. Papers IV and V extend these insights to the rewarming phase through trajectory-based monitoring hypotheses.
5. Paper VI explores whether structured triage symptom data can support earlier diagnostic workflow without being conflated with patient need.

5.2 Integrated summary of findings

Across the six studies, early objective indicators – such as triage category, admission body temperature, selected laboratory parameters, and short-term warming dynamics – were associated with early critical outcomes or indicators of workflow delays (Table 11). These indicators are situated at various points in the translational process: from the triage-level prognostic framework (which is the early risk indicator best supported by internal

data, Paper II), through the descriptive clarification of staging criteria and vulnerability patterns (Paper III), through the early laboratory basis of hyperthermia (Paper I), to the monitoring of the exploratory warming phase (Papers IV–V) and the workflow-sensitive digital prediction of diagnostic demand (Paper VI). Both extremes share the same clinical imperative: early recognition and timely intervention. In accordance with this logic, Paper I focuses on hyperthermia, suggesting that, in this small cohort, early biochemical abnormalities may provide a more useful bedside severity signal than temperature alone. Papers II–V provide a more comprehensive overview of the hypothermic aspect, addressing triage-level indicators and fine-tuning the rewarming phase.

Table 11. Summary of key findings, their potential practical relevance, and implementation status.

Implementation status distinguishes findings that can already inform bedside vigilance or low-threshold testing from findings that remain exploratory and should not yet be protocolised without prospective external validation.

Work	Key finding	Potential practical relevance	Implementation status and evidence maturity
Heat stroke (n=8)	ED mortality 37.5%; admission pH, K^+, ionised calcium, lactate, and $PaCO_2$ were significantly associated with ED mortality	Heat stroke anchors the hyperthermic side of the same front-end ED logic; early laboratory panel may help identify patients requiring rapid escalation in temperate-climate settings	Ready now as a low-threshold trigger for ABG/electrolyte testing and escalation awareness; not ready as a standalone prognostic model
Hypothermia triage model (n=131)	Triage AUC 0.683; triage+temperature AUC 0.740 for ED death/ICU admission	Triage category can be repurposed as a prognostic scaffold; adding temperature yields improved internal discrimination in a single-centre cohort	Closest to implementation; requires external prospective validation before rule-based escalation
Hypothermia comorbidity & staging (n=125)	ED mortality 18.4%; consciousness level frequently diverged from temperature-defined severity—30% of Stage III and 18% of Stage IV patients were fully alert	Mental-status-based staging is unreliable in heterogeneous urban cohorts; emphasise objective temperature measurement, documentation of measurement site, and pattern-aware interpretation	Ready now to caution against consciousness-based staging alone; not ready for individual risk prediction
Rewarming biomarker pilot (n=18)	Significant paired biomarker changes during rewarming consistent with haemodilution and inflammation; patterns more pronounced in critical courses	Dynamic monitoring during rewarming may identify deterioration; supports larger prospective validation	Exploratory only; requires larger prospective cohorts with standardised sampling windows
Coagulation VET pilot (n=16)	ECA-CT and ECA-CFT prolonged in critical courses at admission; significant shortening after rewarming	Coagulation abnormalities during hypothermia and rewarming may be detectable in the early ED course; VET may complement routine tests	Exploratory only; requires validation against bleeding/thrombotic endpoints

Work	Key finding	Potential practical relevance	Implementation status and evidence maturity
ML lab ordering (n=3,925)	Models predicted selected lab orders with moderate-to-strong discrimination and clinically meaningful assay-dependent projected time savings	Patient-generated triage data may support earlier diagnostics if prospectively validated; governance is required to prevent over-testing, bias amplification, and alert fatigue	Exploratory only; requires governance-first prospective impact testing before deployment

5.3 Methodological considerations and limitations

When interpreting the results, it is essential to take methodological limitations into account. In the absence of external validation, neither model was tested on an independent cohort or at another institution. The hypothermic triage model (Paper II) was based on a single-centre cohort with internal validation and calibration, while the machine learning model (Paper VI) employed nested cross-validation. Neither approach demonstrates generalisability to external settings. All studies were conducted in a single university emergency department, with partial overlap in the study periods. This limits the extension of the results to other institutions, different climatic conditions, and healthcare systems with varying patient demographics and triage practices. Pre-hospital data were missing from the databases. Factors such as exposure time, ambient temperature, initial GCS score recorded by paramedics, and pre-hospital interventions could likely improve predictive accuracy as moderators. The retrospective studies (Papers I–III) inherently carry the limitations of registry-based data, including selection bias due to incomplete case recording, non-random missing data, and the fact that clinical documentation was not prepared for research purposes. Furthermore, nutritional status — including body mass index, albumin, and markers of micronutrient deficiency — was not systematically recorded in any of the included cohorts. Homelessness, which affected 44.0% of the hypothermia population (Paper III), was documented as a descriptive variable rather than modelled as a risk factor, despite likely serving as a proxy for a broader vulnerability cluster encompassing malnutrition, prolonged exposure, delayed discovery, and limited adaptive capacity. Future studies should operationalise housing instability and nutritional assessment as structured covariates to determine whether they independently predict critical outcomes or act primarily through interaction with comorbidity burden and exposure duration. The issue of temperature measurement requires consideration. In hypothermia cohorts, tympanic temperature was used as a substitute for core temperature, but this may result in systematic negative bias, as tympanic values typically underestimate

actual core temperature in severe hypothermia, especially below 30 °C [29]. This weakens the relationship between clinical stage and actual physiological severity. The study on heat stroke, as well as the low sample sizes of the prospective pilot studies, essentially gave the analyses a hypothesis-generating character, and the handling of multiple comparisons also remained limited. In Paper IV, we applied false discovery rate (FDR) correction only to a few initial comparisons, while in Paper V, we conducted paired coagulation and viscoelastic analyses using an exploratory approach. However, this procedure carries an increased risk of Type I error. Furthermore, the pilot sample sizes in Papers IV–V did not allow for meaningful subgroup analyses. This limitation also applies to time-related effects: in both physiological pilot studies, the time elapsed until sampling in the warmed state could have influenced the magnitude of the observed changes. The available sample sizes were too small to distinguish biological processes from differences arising from warming rates or sampling logistics. In Paper IV, we were unable to stratify the significant decrease in blood glucose levels observed during warming by diabetes status, although the interaction between chronic glycaemic dysregulation and blood glucose shifts caused by hypothermia is yet another clinically relevant issue that requires targeted investigation. Similarly, in Paper V, it was not possible to subgroup the VET parameters according to comorbidity profiles. Thus, it is currently unknown whether conditions such as chronic liver disease, heart failure, or chronic alcohol consumption modify the extent of hypothermia-related coagulation disorders. To answer this question, larger cohorts with detailed comorbidity data—and possibly machine learning-based phenotyping—will be required. Regarding Paper V, it should be noted that the observed differences and associated changes do not exclusively reflect hypothermia-specific coagulopathy. The physiological effects of rewarming, resuscitation interventions, and variability in measurement temperature also play a role, given the fixed measurement temperature of 37 °C. In the absence of clinical bleeding or thrombotic endpoints, the practical significance of the variations observed in ecarin-based clotting times remains limited. Any proposed threshold values or dynamic patterns must be validated in larger, preferably multicentre cohorts, using predefined primary endpoints. Finally, a composite endpoint consisting of emergency department mortality or intensive care unit admission—while a reasonable compromise between feasibility and clinical relevance—may mask the underlying diverse mechanisms of deterioration, whether refractory

hypothermia or secondary organ failure. In the field of machine learning, predictions regarding clinician laboratory orders are influenced by local clinical practices, which carries the risk of perpetuating existing biases. It is important to emphasise that models trained on the ordering patterns of a specific institution cannot necessarily be applied elsewhere without recalibration. Next steps should include evaluating the models based on patient-centred outcomes. Additionally, regulatory frameworks must be established to avoid unnecessary testing and to prevent performance disparities among subgroups based on age, gender, language skills, or clinical severity. Finally, it must be noted that all our studies were observational in nature, meaning that the identified correlations—including differences between triage-based discriminative estimates and biomarker trajectories—do not prove a causal relationship. These results alone do not prove that intervention based on these markers would improve patient outcomes. To definitively establish clinical benefit, it is essential to use interventional study designs, such as stepped-wedge cluster-randomized trials.

5.4 Contextualisation in international literature

Our hypothermia findings resonate with, and further amplify the expanding body of research that casts doubt on the reliability of consciousness-based severity assessment within diverse emergency cohorts. Pasquier and colleagues evaluated the Swiss staging system based on case reports and hospital data. Their analysis revealed a telling discrepancy: clinical observations aligned with actual core temperature categories in only about 61% of instances [27]. The present study adds three practically relevant observations to this line of evidence. Firstly, it describes substantial consciousness–temperature divergence in a real-world urban emergency cohort, in which drug-related consciousness disorders, intoxication, and social vulnerability are also present. This contrasts with the work of Pasquier and colleagues, who examined the original Swiss system using a mixed hospital/literature dataset. Secondly, it suggests that a mandatory general triage system combined with measured temperature may serve as a pragmatic prognostic framework. Thirdly, it provides a clearly described urban emergency dataset that may facilitate future external replication after publication of the relevant manuscripts. The clinical picture of the present group may help explain why consciousness and temperature-defined severity diverged so frequently in this temperate urban cohort:

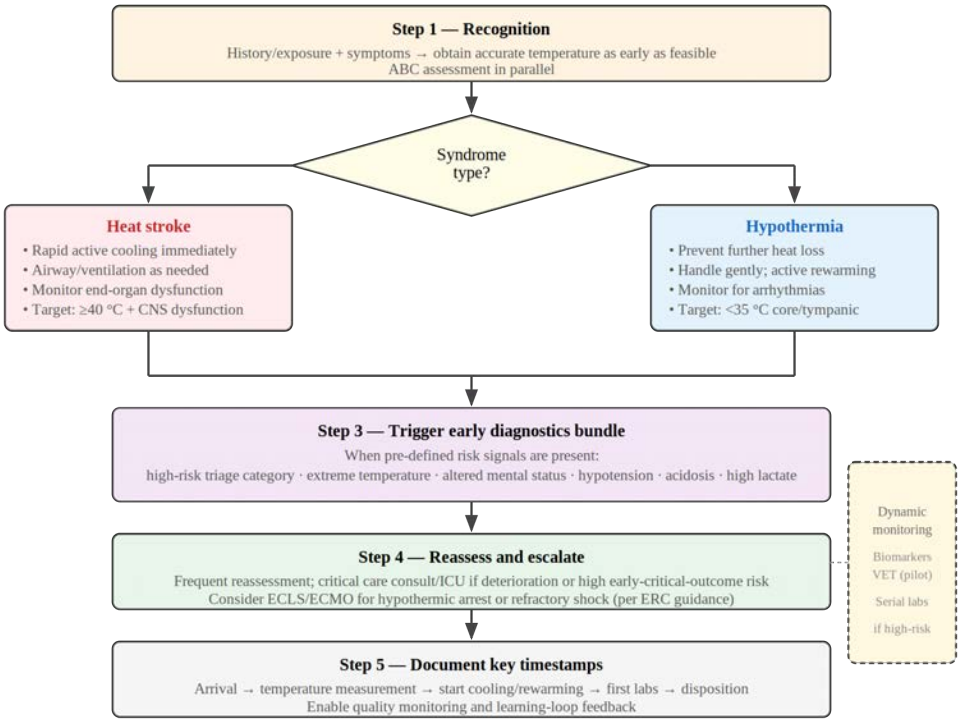
altered mental status was the most common presenting complaint, and patients were found indoors as often as outdoors. In patients suffering from alcohol intoxication or chronic neurological disorders, which are prevalent in this socially heterogeneous population, mental status alone cannot be used as a reliable substitute for body temperature. This reinforces the argument that core temperature measurement — wherever possible, true core measurement — should be considered the primary objective reference point for staging decisions. If tympanic measurement is the only option, it must be clearly documented as a proxy measurement. Current guidelines also advocate the combined use of objective temperature measurement, controlled warming, and structured escalation decisions [29]. Regarding heat stroke, Paper I presents two observations that are mechanistically compatible with the observed early deterioration. The higher levels of ionised calcium observed among non-survivors are biologically consistent with the severe acidosis that is also present. Acidosis reduces calcium binding to albumin and shifts the ionised fraction upward. Consequently, the elevated ionised calcium level in this context may be interpreted as a co-marker of acid-base imbalance rather than as an independent causal factor of mortality. This mechanistic relationship supports considering the ABG profile as a potentially useful early risk indicator. It is important to highlight the seemingly contradictory observation that non-survivors presented with lower core body temperatures. This may reflect heterogeneity in the timing of temperature measurements relative to illness onset and the initiation of on-site cooling, rather than a true inverse relationship between temperature and mortality. These observations are consistent with the possibility that a single temperature threshold may be insufficient for triage or prognostication in heat stroke. Instead, the admission ABG and electrolyte profile can serve as a practical, early reference point for assessing severity. In accidental hypothermia, the "5A" severity scale has been developed to partially address the limitations of stage-based assessment by integrating age, activities of daily living, arrest, acidaemia and albumin into a subsequent risk score based on laboratory data [28]. Our findings suggest that triage category and temperature are useful for the initial ED assessment, whereas more comprehensive scores remain relevant for subsequent decisions (e.g. ward vs intensive care admission, and conventional vs extracorporeal rewarming) once laboratory data are available. The current ERC guidelines explicitly recommend the use of the Swiss staging system when core temperature is not available,

as well as the integration of the HOPE prognostic score into hospital decision-making when assessing ECLS indications [14]. Recent multicentre registry data have begun to reveal correlations between warming rate and outcome [39], the prognostic factors of hypothermic circulatory arrest [40], and the limitations of applying eligibility criteria developed for normothermic circulatory arrest to hypothermic patients [41]. This contributes to an expanding international evidence base that contextualises the early detection framework proposed here and supports the feasibility and clinical relevance of future multicentre hypothermia prognostic research. The NLR results from Paper IV should be interpreted in context. Once patients had reached normothermia, we observed significantly higher NLR values in patients in the critical outcome group, consistent with a more pronounced systemic inflammatory response. This high ratio is the result of both a neutrophil-dominant immune response and low lymphocyte counts. This pattern has also been observed in other severe conditions and is consistent with our understanding of immune dysfunction caused by hypothermia. If this significant difference could be confirmed in a larger patient cohort, the post-warming NLR could serve as a simple bedside indicator for monitoring patients' conditions during this critical early period. However, due to the small sample size, lack of statistical adjustments and concurrent presence of other inflammatory markers (elevated CRP and lower haematocrit), we cannot yet draw far-reaching conclusions. Until a comprehensive, prospective study is available, these results should be treated merely as hypotheses worthy of further consideration. Paper VI aligns with the current trend in emergency medicine towards digital triage and decision support systems, while also highlighting a key lesson from the literature on predictive modelling: discriminatory power alone does not guarantee safe implementation. In our cohort, structured symptom recording during triage predicted the selected laboratory orders with moderate-to-strong internal discrimination, while the separate ordering-latency analysis suggested a substantial potential reduction in the time to order. Nevertheless, calibration, transferability testing, integration into the workflow, and ensuring continuous monitoring remain essential for practical application [23, 24, 32, 33, 42].

5.5 Implications for ED protocols: a proposed decision-support framework

After a detailed review of the results, a practical, two-step emergency decision-support framework can be outlined. This model does not replace clinical judgment, but rather serves as a conceptual "safety net" for escalation decisions in everyday clinical practice. The corresponding escalation elements are summarised in Table 12, and the two-step logic is illustrated in Figure 11. In the management of hypothermic patients, this framework is not a rival to existing extracorporeal prognostic tools, but rather a complement to them, in a clearly sequential order. While triage and temperature data serve as an early warning system upon arrival in the emergency department, the HOPE score pertains to a later stage of decision-making—at the hospital/ECLS level—when more detailed physiological and laboratory results are available. The proposed algorithm is therefore not an alternative to HOPE-based prognosis, but rather the very step that identifies which patients require this second-level assessment [14]. A key difference in this framework is that the early laboratory panel belongs to the refinement step, not the triage step. Triage-level risk flags rely exclusively on variables obtainable within minutes of arrival — measured temperature, triage category, and clinical red flags — whereas the laboratory panel serves to confirm, quantify, or escalate the risk signal once the initial classification has been made. Conflating these two layers would undermine the operational advantage of the framework, as laboratory turnaround times would re-introduce the very delays the triage step is designed to circumvent. The monitoring layer of the rewarming phase (Tables 7–8) is based on the pilot results. Differences in rewarming-related biomarker patterns were observed during rewarming to ≥35 °C (Paper IV), while ecarin-based clotting times were prolonged in the critical group in hypothermia and then shortened after rewarming (Paper V). While further validation is required to substantiate these observations, they provide a preliminary rationale for incorporating a biomarker-monitoring component into this conceptual framework. Point-of-care viscoelastic testing, when available at the institutional level, may provide complementary information on coagulopathy beyond routine coagulation screening tests. Any triage-level prediction system must also address the risk of overtesting as a key design consideration from the outset, rather than as an afterthought. When anticipatory laboratory ordering is triggered before physician assessment, each false-positive prediction results in an unnecessary blood draw, reagent cost, and interpretive burden. The clinical operating

point of such models — the threshold at which a predicted probability is converted into an order recommendation — should therefore be calibrated not only for sensitivity but also for the marginal cost of overtesting within the specific institutional context, including downstream effects on alert fatigue and patient trust.



Note: Specific thresholds and bundles should follow institutional policies and current guideline recommendations.

Created for this dissertation.

Figure 11. Conceptual ED escalation algorithm for thermal emergencies. Source: Own figure (created by the candidate).

Conceptual flow showing two escalation layers. Step 1: triage-level risk flags (temperature + triage category + red flags). Step 2: early laboratory refinement panel triggering ICU consultation, advanced cooling/rewarming, and ECLS consideration. Separate decision nodes are shown for heat stroke and hypothermia pathways. Intended as a locally adaptable framework; created by the candidate for this dissertation.

Table 12. Proposed structure of a pragmatic ED escalation pathway for thermal emergencies.

Syndrome	Early triggers (triage-level)	Immediate actions (ED-level)
Heat stroke / severe hyperthermia	Core temperature typically >40 °C with central nervous system dysfunction, or strong clinical suspicion of exertional/classic heat stroke; haemodynamic instability; seizures or coma; high-acuity triage category. Diagnosis should remain clinical and must not rely on temperature alone.	Immediate active cooling; prioritise the fastest feasible method, preferably cold- or ice-water immersion where available; target core temperature <39 °C within 30 min of recognition and, where feasible, a cooling rate ≥0.155 °C/min; avoid dantrolene and routine antipyretics/non-steroidal anti-inflammatory drugs/salicylates; airway/ventilation as needed; early lab panel (blood gas, electrolytes, lactate, renal/liver markers); early ICU consult if profound acidaemia/hyperkalaemia/hyperlactataemia or organ-failure signals are present [9, 43].
Accidental hypothermia	Temperature <35 °C + high-acuity triage category; altered mental status not explained; hypotension/shock; arrhythmia risk; concern for prolonged exposure or delayed discovery	Measure core temperature with a low-reading thermometer whenever feasible; if core temperature cannot be measured, use the Swiss Staging System as an estimate; active external and/or internal rewarming tailored to haemodynamic stability; early lab panel; direct transfer to an extracorporeal life support (ECLS)-capable centre for hypothermic arrest or imminent-arrest features (heart rate <45/min, systolic blood pressure <90 mmHg, ventricular arrhythmia, or core temperature <30 °C); use HOPE as a second-level in-hospital prognostic tool once extracorporeal rewarming is under consideration, rather than as a replacement for triage-level front-end flagging [13, 14].
Rewarming phase (high-risk subgroup)	High-risk defined by Step 1 + abnormal early labs or clinical features suggestive of limited physiological reserve	Dynamic rewarming-phase monitoring (repeat biomarkers and viscoelastic testing where available); reassess for evolving organ failure; anticipate disposition barriers; ensure warming/cooling continuation during transfer/boarding

5.6 Implementation, governance, and evaluation

In training, the “triage plus temperature” principle is suitable for illustrating decision-making in uncertain situations; in specialist training, the kinetics of biomarkers can provide a structured foundation; and in the training of paramedics and emergency medical technicians, the standardisation of tympanic membrane temperature measurement and the use of automatic alert thresholds should be incorporated. The first step in practical implementation is the standardisation of measurement methods at the institutional level and the mandatory documentation of the measurement location. When accelerating

workflows based on machine learning, it is essential to clearly define where the algorithm's recommendation ends and automation begins, while also striking a balance between time savings and unnecessary additional checks. When measuring efficiency, it is essential to track the time elapsed from the start of care to its conclusion, the speed of intensive consultations, resource utilisation, and adverse events. It is also essential that we be transparent with patients: the information provided to them must clearly state that an algorithm may be involved in requesting laboratory tests. Finally, when planning the capacity of the emergency department, the impact of expected periods of extreme weather must be considered. Operational measures may include reserving hospital beds in advance, ensuring rapid access to cooling and heating equipment, and implementing overload protocols during heat waves or prolonged periods of freezing weather.

5.7 Future directions

The next important step is to conduct a prospective, multicentre study of the "triage plus temperature" approach to accidental hypothermia in different EDs. A stepped-wedge cluster-randomised study in two or three domestic EDs with different patient compositions would be one strong design for the feasibility of integrating the approach into the workflow. In addition to indicators of discrimination, the use of decision-curve analysis and calibration diagrams is recommended in future validation studies. Although Paper II demonstrated robust internal results in terms of discrimination and calibration, the real-world transferability of the models between institutions will inevitably depend on local patient composition, measurement practices, and resource constraints. Consequently, future research should pair external testing with prospective impact analysis, balancing patient-centred outcomes with granular process indicators—such as the speed of initiating thermal regulation, the timing of intensive care consultations, and the overall efficiency of patient disposition. Paper I demonstrates proof-of-concept for emergency department-level outcome characterisation but does not have sufficient statistical power to derive prognostic models. Prospective multicentre registration of exertional and classic heat stroke cases in Central European emergency departments is necessary. Ideally, this should be accompanied by standardised core temperature measurement, supplemented by serial biomarker panels and systematic organ damage documentation. This will help to clarify whether the triage-plus-temperature signal

observed in hypothermia can be transferred to the hyperthermic spectrum. In view of the increasing frequency of extreme heat waves in continental Europe and the scarcity of emergency department-level heat stroke mortality data from the region, the establishment of such a registry would address a significant evidence gap and inform the heat stroke layer of the proposed decision support framework (Table 12). This would also help align that pathway with recent Society of Critical Care Medicine (SCCM) guidance on heat stroke management [43]. Secondly, the pilot studies (Papers IV–V) raise mechanistic hypotheses that require further investigation, such as changes in biomarkers during rewarming or VET patterns in hypothermia. To verify these observations, larger, multicentre cohorts with standardised sampling times and predefined endpoints will be required. It would also be beneficial to clarify which underlying metabolic diseases influence the physiology of rewarming. Future prospective studies should record diabetes status, baseline glycaemic control, and nutritional indicators to determine whether chronic comorbidities indeed modify blood glucose and viscoelastic profiles. Unfortunately, the pilot-sized samples were not suitable for answering this question. Multicentre registry data on hypothermic cardiac arrest, as well as prospective evidence demonstrating for the first time on a large scale the relationship between rewarming rate and survival and neurological outcome in non-cardiac hypothermia, support the view that such efforts are now feasible and clinically productive [39, 40]. By associating these markers with actionable endpoints (arrhythmias, bleeding/thrombosis, organ failure), we can ascertain which laboratory or point-of-care tests possess genuine decision-making value in the emergency department, as opposed to merely descriptive relevance. Integration with ECMO/ECLS registries could further clarify the role of early biomarkers and viscoelastic signals in guiding extracorporeal rewarming decisions, in line with current ERC recommendations [13, 14]. In the specific area of ECLS decision-making, the HOPE prognostic score achieved an area under the curve (AUC) of 0.895 (optimism-corrected to 0.866) in the derivation cohort and 0.825 in external validation [44, 45], which represents strong discrimination. The integration of our triage-level signs with such proven prognostic tools warrants prospective evaluation. Conceptually, the Paper II model and the HOPE score occupy complementary positions: the triage model operates at ED arrival using only triage category and tympanic temperature, while the HOPE score is applied later in the escalation pathway, using hospital-level variables available before

extracorporeal rewarming to support ECLS decision-making. This sequential logic — early triage-level flagging followed by HOPE-guided ECLS decision — has not been prospectively tested but represents a testable hypothesis. Recent multicentre data have also shown that the standard Extracorporeal Life Support Organization (ELSO) eligibility criteria may be too restrictive in cases of hypothermic cardiac arrest, as a 37% survival rate has been documented even among patients who do not meet the traditional criteria [41]. Thirdly, when evaluating digital triage tools as a sociotechnical intervention, it is essential to consider more than just retrospective accuracy. Time savings, over-testing, workload effects, and equity must all be considered [23–25]. Moving forward, it is essential to align research efforts with operational readiness in practice. The heat stroke pathway should be further refined in line with Society of Critical Care Medicine (SCCM) guidance [43]. In addition, credible overload plans for both heat and cold events must be built [30, 46, 47]. Digital triage tools must also be subjected to governance-first evaluation, particularly given that their self-triage accuracy varies considerably [25, 48]. In the narrower field of extracorporeal rewarming, the 2025 ELSO narrative guideline has collated the evidence on ECMO use in accidental hypothermia into a structured patient-selection and management framework, one that fits naturally alongside the escalation logic proposed here [49]. The recently introduced Hypothermic Extracorporeal Life Support Prognosis (HELP) score adds a prognostic layer for non-asphyxia-related hypothermic cardiac arrest following extracorporeal rewarming, covering a subgroup that earlier models handled poorly [50].

6 Conclusions

The dissertation is based on six original studies, and it argues that variables available early in the emergency department – such as triage category, measured temperature, mental status as a risk modifier, and a narrow admission laboratory panel – may support pragmatic risk stratification of thermal emergencies. These findings should be interpreted in the context of the predominantly single-centre design and the inherent limitations of small prospective pilot studies. The integrated results can be summarised as follows:

1. Heat stroke: early emergency department mortality was associated with severe acid-base and electrolyte disturbances, supporting the use of low-threshold ABG and electrolyte testing. However, due to the small sample size, the findings are currently hypothesis-generating.
2. Accidental hypothermia: In our retrospective cohort, the combined use of general triage classification and admission tympanic temperature yielded a higher point-estimate discrimination for early critical outcomes than the hypothermia-specific classifications examined. Despite the overlap in the confidence intervals, the findings support prospective evaluation of a pragmatic emergency-department-level framework. This may support decisions on higher-level care, resource planning, and intensive care consultations, especially when detailed data for accurate staging are not yet available at the time of admission.
3. Staging accuracy and vulnerability: In our heterogeneous urban cohort, consciousness level frequently diverged from temperature-defined severity, supporting the prioritisation of objective temperature measurement—preferably core temperature. If tympanic measurement is used, the measurement site should be documented. Altered mental status should be interpreted as an important risk modifier rather than a substitute for temperature, while acknowledging potential confounding by alcohol use, sedatives, and comorbidity. The combined analysis of comorbidity and drug treatment provides a promising starting point for understanding differences between patients, but the relationship with mortality was not significant in our cohort, so confirmation requires a larger sample size.
4. Mechanism and monitoring: In two original, prospective pilot studies, we used paired biomarker sampling and point-of-care VET monitoring during the emergency department rewarming phase of accidental hypothermia. During this

phase, we observed trajectories consistent with haemodilution, inflammation, and hypothermia-associated coagulopathy.

5. Digital triage-based implementation: Our simulations, conducted among adult patients classified as MSTR III–V who completed the questionnaire, show that models based on patient-reported symptoms can predict certain laboratory orders with moderate to strong internal discrimination. If prospectively validated, this could translate into clinically meaningful time savings. At the same time, as modelling clinical decisions does not equate to determining actual medical needs, strict professional governance, continuous model drift monitoring, and subgroup-level performance auditing are therefore essential to ensure safe implementation. In addition, a prospective, critical assessment of the risk of overdiagnosis, the additional burden on staff, and the impact on actual patient outcomes is also essential.
6. What can already inform practice is a front-end ED approach that emphasises early temperature measurement and documentation of the measurement site, avoids using consciousness as a surrogate for temperature-defined hypothermia severity, uses triage category plus admission temperature as an early risk signal in accidental hypothermia, and applies low-threshold ABG/electrolyte testing in suspected heat stroke when severe physiological derangement is a concern.
7. What remains exploratory is the routine operational use of rewarming-phase biomarker trajectories, viscoelastic thresholds, and machine-learning-based anticipatory laboratory ordering. These components are promising, but they should still be regarded as hypothesis-generating or implementation-oriented concepts until prospective multicentre validation, calibration assessment, and impact studies demonstrate net clinical benefit, acceptable overtesting burden, and safe governance.

The dissertation presents a cohesive emergency framework, integrating the early recognition of patients with targeted risk assessment and escalation decisions, from the moment they arrive in the ED. The model's key strength is the simplicity of integrating the MSTR triage category and admission temperature in the context of accidental hypothermia. The remaining studies provide a contextual framework within the domains of hyperthermia, rewarming physiology and workflow-sensitive digital support.

Subsequent phases should involve multicentre testing to determine whether acting on these early signs can accelerate care, improve escalation and enhance patient flow in emergency settings, which are becoming increasingly affected by climate-related thermal stress.

7 Summary

This dissertation summarises six original studies conducted in an emergency department in Budapest. The studies analyse how low-threshold triage variables, and a limited early laboratory panel, can improve risk stratification in thermal emergency conditions and aid in escalation decision-making in emergency care. In the heat stroke study, three out of eight patients died in the emergency department. Early mortality was associated with significant acid-base and electrolyte disturbances, as indicated by admission arterial blood gas analysis. In cases of accidental hypothermia, the combination of the mandatory triage category and admission body temperature showed the highest point-estimate discrimination for early critical outcomes. In a second group of patients, levels of consciousness often differed from the temperature-defined severity — in a cohort with frequent alcohol use, sedatives, and psychiatric comorbidity — alongside characteristic patterns of comorbidity and drug co-occurrence. According to the pilot data, there were differences in the biomarker and viscoelastic profiles during the rewarming process, which were indicative of the early clinical course. A machine learning model built on triage-level symptom data was able to predict laboratory orders in a simulated setting, with the potential to reduce the interval from triage to first laboratory order by one to two hours.

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9 Bibliography of the candidate's publications

The dissertation is based on the following publications and manuscripts (published, under review, or submitted) available at the time of dissertation submission. In the works forming the basis of this dissertation, the candidate (KÁ) served as first author (Papers I–V) or shared first author (Paper VI) and made a substantial contribution to study conception, literature review, data collection/curation, statistical analysis, interpretation, and drafting, as documented in the author-contribution statements of the individual manuscripts. Co-authors contributed to study design, clinical data access, critical revision, and supervisory oversight as detailed in each publication.

9.1 Publications and manuscripts forming the basis of the dissertation

1. Paper I (Published): Ádám K, Berényi T, Melicher D, Fenyves BG, Gaál S, Varga C. Risk factors of early death in heat stroke and the challenges of emergency care in

Hungary - a case series study. Int J Emerg Med. 2024;17(1):150. doi: 10.1186/s12245-024-00743-w.

2. Paper II (Published): Ádám K, Stelkovics A, Zadravecz-Heider B, Melicher D, Bognár Z, Farkas BV, Fenyves BG, Gaál-Marschal S, Varga C. Accidental hypothermia in emergency care: multifactorial triage-based prediction of early critical outcomes in a temperate-climate cohort. PLoS One. 2025;20(10):e0334328. doi: 10.1371/journal.pone.0334328.
3. Paper III (Published): Ádám K, Stelkovics A, Farkas BV, Hetzman LT, Bognár Z, Fenyves BG, Vörös B, Varga C. Accidental hypothermia in a temperate urban emergency department: comorbidity, pharmacotherapy, and clinical staging patterns. Am J Emerg Med. 2026;105:169–176. doi: 10.1016/j.ajem.2026.04.028.
4. Paper IV (Under review): Ádám K, Stelkovics A, Farkas BV, Fenyves BG, Sóti Á, Imecz J, Fazakas J, Garami A, Varga C. Serial blood gas and laboratory changes during emergency department rewarming in accidental hypothermia: a prospective observational pilot study. Status: Under review at Heliyon (submitted February 2026).
5. Paper V (Submitted): Ádám K, Stelkovics A, Farkas BV, Fenyves BG, Hetzman LT, Fazakas J, Garami A, Varga C. Viscoelastic parameters measured at 37 °C during accidental hypothermia and after rewarming: a prospective emergency department pilot study. Status: Submitted to European Journal of Emergency Medicine (March 2026).
6. Paper VI (Under review): Schiegl A*, Ádám K*, Barta AG, Sóti Á, Stelkovics A, Vad L, Mendik P, Fenyves BG, Varga C. Accelerating laboratory orders in the emergency department using patient-reported symptoms at triage. *These authors contributed equally as shared first authors. Status: Under review at IEEE JBHI (submitted March 2026).

9.2 Other publications by the candidate

- Ádám K, Barta L, Xantus G, Fenyves BG, Varga C. A Rövidített Sürgősségi Osztályos Betegelégedettségi Skála hazai validációja. Orv Hetil. 2025;166(3): 109–115. doi: 10.1556/650.2025.33193.

- Ádám K, Belső A, Hegyi K, Varga C, Borsos M, Xantus G. Sürgős teendő, vagy időrablás? Magas vérnyomással jelentkező 65 év feletti betegek ellátása a sürgősségi osztályon. Orv Hetil. 2025;166(50):1975–1982. doi: 10.1556/650.2025.33443.
- Túri BZ, Ádám K, Szakáll A, Fenyves BG, Kálmán Z, Gaál-Marschal Sz, Mészáros H, Imecz J, Varga C. ST-Segment Elevation in Lead aVR in Acute Intracranial Pathologies: A Diagnostic Pitfall? J Emerg Med. 2026;80:54–59. doi: 10.1016/j.jemermed.2025.10.023.
- Túri BZ, Ádám K, Fenyves BG, Varga C. Reply to the Letter to the Editor: ST-Segment Elevation in Lead aVR and Acute Intracranial Pathologies: Reconsidering the Association. J Emerg Med. 2026;80. In press. doi: 10.1016/j.jemermed.2026.01.020.
- Ádám K, Varga C, Fenyves BG, Hegyi K, Kostyál L, Finta E, Kanizsai PL, Lelovics Zs, Xantus G. Mozgásszervi eredetű mellkasi fájdalmat felismerő klinikai predikciós modell fejlesztése: Prospektív pilotvizsgálati elképzelés. Orv Hetil. 2026;167(5):180–187. doi: 10.1556/650.2026.33484.
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