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Investigation of Pathophysiology, Intensive Care Procedures, Prognostic and Mortality Factors in Conditions Requiring Cardiopulmonary Resuscitation

Prognostication and Age–Treatment Interactions

in Out-of-Hospital Cardiac Arrest

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List of abbreviations

AED: automated external defibrillator
ALS: advanced life support
ARD: adjusted risk difference
AUC: area under curve
BLS: basic life support
CAC: cardiac arrest center
CAHP: cardiac arrest hospital prognosis
CI: confidence intervals
CPC: cerebral performance category
CPR: cardiopulmonary resuscitation
CV: cross validation
DOI: digital object identifier
EMS: emergency medical services
ERC: European Resuscitation Council
ESICM: European Society of Intensive Care Medicine
EU: European Union
FDR: false discovery rate
FN: false negative
FP: false positive
GCS: Glasgow Coma Scale
HNAS: Hungarian National Ambulance Services
ICU: intensive care unit
IHCA: in-hospital cardiac arrest
NNT: number needed to treat
No: number
OHCA: out-of-hospital cardiac arrest
OR: odds ratio
PCAS: post cardiac arrest syndrome
PEA: pulseless electrical activity
PIF: potential impact fraction
pp: percentage points

PRISMA: preferred reporting items for systematic reviews and meta-analyses

PSS: prognostic scoring system

RCT: randomized controlled trial

ROC: receiver operating characteristic

ROSC: return of spontaneous circulation

SCA: sudden cardiac arrest

SCD: sudden cardiac death

SIRS: systemic inflammatory response syndrome

TN: true negative

TP: true positive

TTM: targeted temperature management

VF: ventricular fibrillation

VT: ventricular tachycardia

WLST: withdrawal of life-sustaining treatment

1. Introduction

1.1. Definition and significance of sudden cardiac death

Sudden cardiac death (SCD) is one of the leading causes of cardiovascular mortality and a major public health problem. Although multiple definitions of SCD have been applied historically, contemporary research most commonly defines SCD as a natural death of presumed cardiac aetiology in which - when the event is witnessed - no more than 1 hour elapses between the onset of initial symptoms and the terminal clinical event, i.e., cardiac arrest. In unwitnessed deaths, cases may be classified as SCD when the individual was last seen alive and in apparent normal health within 24 hours preceding discovery of the victim's body. (1 - 4)

Different historical definitions of SCD limit comparability across studies, and the frequent conflation of SCD with sudden cardiac arrest (SCA) further complicates interpretation. SCA refers to an abrupt cardiac arrest—often within 1 hour of symptom onset—that may be reversible with timely resuscitation. (3) Epidemiological classification remains challenging because cardiac aetiology is rarely confirmed by autopsy, and extending the symptom-to-arrest time window increases SCD case counts while reducing the proportion attributable to cardiac disease. (3, 5) Sudden cardiac arrest events are commonly categorized as out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA), reflecting differences in etiological distributions, care pathways, and prognosis. (6) Additional heterogeneity stems from differences in data collection, including case definitions, ascertainment procedures, and outcome verification. To standardize reporting, the Utstein guidelines for OHCA and IHCA outcomes have been issued since the early 1990s and are periodically updated to harmonize data collection and facilitate inter-study comparability. (7, 8)

The epidemiological burden of SCD is high: of an estimated 17 million cardiovascular deaths globally each year, approximately one quarter (4-4.5 million deaths) are attributed to SCD. (9) In the United States and other industrialized countries, SCD may account for nearly 15% of all-cause mortality. (1, 2, 10, 11) Despite substantial methodological and technological advances in basic and advanced cardiopulmonary resuscitation, post-resuscitation critical care, and rehabilitation, outcomes following sudden cardiac arrest and sudden cardiac death remain poor, with persistently low survival and correspondingly high mortality.

1.2 Incidence of out-of-hospital cardiac arrest

The incidence of OHCA spans a wide and heterogeneous range (31-243 cases per 100,000 person-years) according to international literature and studies, both in Europe and in the United States. (4, 5, 11 – 22)

Incidence estimates depend on the definition applied for SCA, as well as on geographic and demographic factors and on the data source used. Notably, OHCA case numbers can be more readily aggregated and estimated from emergency medical service (EMS) resuscitation reports (Utstein formulas).

Reported OHCA case numbers in the United States showed a decreasing trend in the last 25 years: according to data published in 2001, the occurrence of OHCA was estimated at 400,000-450,000 cases per year; however, later publications suggested that this figure represented an overestimation, reporting 141,900-178,000 cases per year in 2004 and 180,000-250,000 cases per year in 2008. (11, 17, 19) This apparent decline may be attributable to changes in definitions and exclusion criteria, as well as to advances in primary cardiovascular prevention and improvements interventional cardiology care.

Across the EuReCa studies, OHCA incidence in Europe shows marked between-country variation but is stable over time. The mean incidence remained broadly unchanged across the 8-year EuReCa period. (20, 21, 22)

In Hungary, epidemiological data have been available since 2003 based on Utstein templates completed by the Hungarian National Ambulance Service (HNAS). According to data 13,767 OHCA were recorded over a 30-month period, corresponding to an estimated national incidence of 55 cases per 100,000 population per year. (23, 24) Hungary's participation in EuReCa program provided better structured, registry based data about OHCA incidence. The incidence of OHCA in Hungary showed increasing trend in the three (2014, 2017, 2022) EuReCa registry (from 122 to 243 cases per 100,000 population per year). (20, 21, 22)

1.3. Incidence of in-hospital cardiac arrest

Literature provides only uncertain estimates regarding the burden of in-hospital sudden cardiac death and resuscitation events, including attempted resuscitations. The incidence of IHCA can be estimated either as the number of events per hospital bed or as the number of events per hospital admission. (25) To improve comparability, the European Resuscitation Council (ERC) continues to recommend Europe-wide implementation of

the Utstein reporting standards for in-hospital cardiac arrest. These standards specify reporting incidence as the number of treated IHCA per 1,000 hospital admissions, excluding arrests occurring in the emergency department. (26)

Several recent studies align with earlier European data, consistently indicating an incidence in the range of approximately 1.5-2.8 per 1,000 hospital admissions. (27 - 32)

In Hungary, only limited data are available on in-hospital cardiac arrests: the annual number of IHCAs is estimated at approximately 3,000-4,000 cases; however, robust epidemiological quantification is difficult due to non-standardized hospital documentation. (33)

1.4. Age and cardiac arrest

Ageing is a long-term demographic trend affecting all European Union (EU) countries. Current Eurostat data indicate not only an overall increase in the proportion of older adults, but also a progressive ageing within the elderly population itself. Epidemiological projections further suggest that the proportion of elderly individuals among OHCA patients will increase in the near future. (34) Between 2019 and 2050, the number of people aged ≥ 65 years in the EU is projected to rise substantially, from 90.5 million to 129.8 million leading to healthcare overload. (35, 36)

Age is a major determinant of both the incidence and outcomes of SCA: risk increases with advancing age, and older adults account for the large majority of OHCA cases ($>80\%$). (37, 38)

Across studies, older age is consistently associated with lower survival and poorer neurological outcomes after OHCA. Compared with older patients, younger individuals more frequently achieve return of spontaneous circulation (ROSC), survive to hospital discharge, and have favourable neurological recovery. Survival rates decline markedly with age- reported to decrease from 16.7% in patients <20 years to 1.7% in those aged 95-99 - with a comparable deterioration in good neurological outcomes. (39 - 42)

In clinical practice, particularly when pre-arrest history and arrest circumstances are unknown, treatment intensity may be influenced disproportionately by chronological age, including decisions to terminate resuscitation or to limit post-resuscitation intensive care. Older patients may receive less aggressive resuscitation and post-arrest management, which may contribute to poorer outcomes. (39, 43) Nevertheless, age alone should not be used as the sole criterion for treatment decisions. Although prognosis worsens with

increasing age, there is no specific age threshold beyond which meaningful recovery is impossible, and selected elderly patients - especially those presenting with shockable initial rhythms - can still achieve favourable outcomes. (44 - 46)

1.5. Sex and cardiac arrest

The incidence of SCA is higher in men than in women; however, the magnitude of this sex-related risk difference appears to diminish with advancing age, after which male and female incidence trajectories tend to run more in parallel, broadly mirroring sex patterns seen in other cardiovascular diseases.

In a nationwide Danish study of 54,028 SCA cases, incidence rates increased with age in both sexes and were consistently higher in men across adult age groups; the largest male-female disparity was observed between 35 and 50 years. Men also died younger than women (mean age 71 vs 79 years). In younger populations, a nationwide analysis similarly reported that SCA occurs more frequently in males than females. (47, 48)

Beyond incidence, sex differences extend to clinical and circumstantial characteristics: women with SCA are typically older at the time of death, less likely to have a documented prior cardiac diagnosis, and less likely to have coronary artery disease identified at post-mortem examination; SCA in women is also more likely to occur at home or during sleep and to be unwitnessed. (49)

1.6 Cause and etiology of sudden cardiac arrest

Cardiac arrest starts mainly with cardiac arrhythmia. Arrhythmic mechanisms are commonly categorized by rhythm as to be shockable rhythms - ventricular tachycardia (VT) and ventricular fibrillation (VF) - or non-shockable rhythms, including pulseless electrical activity (PEA), asystole, and persistent bradyarrhythmia. Transient ischemia in a previously scarred or hypertrophied myocardium, disturbances in fluid balance, electrolytes, or hemodynamic; fluctuations in autonomic nervous system activity; and transient electrophysiological effects of drugs or other chemicals (e.g., proarrhythmic agents) can all disrupt myocardial electrophysiological stability and trigger electrical instability and arrhythmias. (2, 50)

The aetiology of SCA is highly heterogeneous (see details in Table 1.). The main causes can be classified into: coronary artery disease, other structural cardiovascular diseases,

primary electrical causes and non-cardiac causes. Approximately 70% of SCA cases are attributable to coronary artery disease, and about 10% to cardiomyopathies. (50)

Marked age-related differences are observed in the distribution of underlying aetiologies. In younger populations, genetically determined and congenital conditions predominate, including channelopathies, hypertrophic cardiomyopathy, congenital long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, congenital coronary artery anomalies, mitral valve prolapse, and Brugada syndrome; myocarditis and exposure to medications or other substances are also common triggering and mandatory contributors of arrhythmogenesis. In older populations, degenerative cardiac diseases are predominant, most notably coronary artery disease, heart failure, and valvular heart disease. (2, 3)

Table 1. Major causes of sudden cardiac arrest.

Cardiac condition			Non-cardiac condition
Coronary artery disease	Other structural heart disease	Primary electrical causes	
• Atherosclerotic coronary artery disease • Coronary artery embolism, vasospasm, arteritis, dissection • Congenital anomalous coronary artery	• Hypertrophic cardiomyopathy • Arrhythmogenic right ventricular cardiomyopathy • Dilated cardiomyopathy • Myocarditis • Infiltrative cardiomyopathy • Valvular heart disease • Congenital heart disease • Acute pericardial tamponade • Acute myocardial rupture	• Congenital or acquired long QT syndrome • Short QT syndrome • Brugada syndrome • Wolff-Parkinson-White syndrome • Catecholaminergic polymorphic ventricular tachycardia • Early repolarization syndrome • Complete heart block • Commotio cordis	• Pulmonary embolism • Intracranial haemorrhage • Aortic dissection • Hypovolemia • Drowning • Illicit stimulants or respiratory depressants • Upper airway obstruction • Medications • Tension pneumothorax • Sudden infant death syndrome (SIDS) • Sudden unexplained death in epilepsy (SUDEP)

1.7. Treatment of sudden cardiac arrest

The “chain of survival” concept originated from Friedrich Wilhelm Ahnefeld and Peter Safar, highlighting a sequence of time-critical interventions that collectively increase the likelihood of survival after cardiac arrest. (51, 52) Although visual representations have changed over time, the underlying principles of the chain have remained largely consistent.

The ERC first presented the chain of survival in a four-link format in the 2005 Guidelines, defining the essential elements for successful resuscitation: early recognition and activation of emergency response, immediate bystander cardiopulmonary resuscitation (CPR), rapid defibrillation, and timely advanced life support (ALS) combined with standardized post-resuscitation care. (53) The optimal outcome require that all steps occur promptly and effectively. The term “chain of survival” is now widely used internationally in resuscitation education, public awareness, and research (Figure 1.).



Figure 1. The chain of survival. (54) Available from: <https://www.erc.edu/for-everyone/learn-cpr/chain-of-survival/>

The ERC Guidelines 2025 continue to recommend a four-link chain to preserve clarity and consistency, while expanding and rearranging the content of the original links. This core chain is intended to be applicable across arrest aetiologies and locations, and for all age groups. (54)

CPR refers specifically to the technical components of cardiopulmonary resuscitation (chest compressions and ventilation), whereas “resuscitation” is a broader umbrella term encompassing the full spectrum of associated skills and interventions. Basic Life Support (BLS) comprises early initiating of the chain of survival, prompt delivery of high-quality chest compressions with effective ventilation, BLS-AED means additional early use of an automated external defibrillator (AED). (55)

Adult Advanced Life Support (ALS) includes additional, advanced interventions delivered by healthcare professionals on top of BLS and AED use, with the greatest benefit when initiated as soon as possible after cardiac arrest. ALS covers the prevention and management of both IHCA and OHCA, application of the ALS algorithm, manual defibrillation, airway management during CPR, administration of resuscitation medications, and treatment of peri-arrest arrhythmias. (56)

1.7.1. Basic life support

Basic life support can be defined as immediate, non-invasive emergency care aimed at sustaining life, including cardiopulmonary resuscitation, haemorrhage control, stabilization of fractures and suspected spinal displacement, and provision of essential first aid. Since these interventions are frequently lifesaving, the earliest possible initiation is critical - particularly prompt CPR and early use of an AED (see Figure 2.).

The actual ERC Guidelines about BLS are focusing on rapid recognition and dispatcher-supported action: emergency call handlers play a central role in identifying cardiac arrest (especially when callers report unresponsiveness with abnormal/agonal breathing) and in delivering clear, structured dispatcher-assisted CPR instructions. (55) Dispatcher-assisted CPR is widely implemented and recommended for suspected cardiac arrest. Compared with situations in which no CPR instructions are provided, dispatcher-assisted CPR is associated with higher survival to hospital discharge and greater survival to discharge with favourable neurological outcome. (57, 58)

Knowledge and application of high-quality chest compressions remained the cornerstone of layperson BLS, as compression quality is a key determinant of survival after resuscitation. According to ERC recommendations, the principal characteristics of high-quality chest compressions are as follows: compression depth of 5-6 cm; compression rate of 100–120 compressions per minute; minimized interruptions before and after

defibrillation (<10 seconds); CPR should be performed on a firm surface whenever feasible; complete chest recoil and a 1:1 compression-to-release ratio. (55)

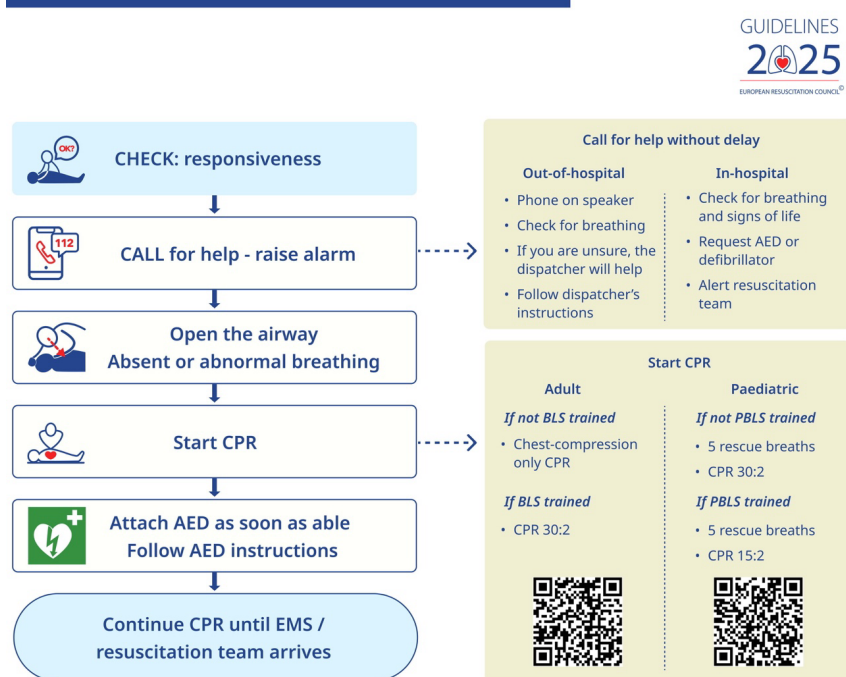


Figure 2. Basic life support algorithm (55) Available from: <https://www.erc.edu/science-research/guidelines/guidelines-2025/guidelines-2025-english/>.

ERC also reinforces early defibrillation through widespread public-access AED programmes. Early defibrillation within 3-5 minutes of collapse can increase survival rates to as high as 50-70%. Registry data shows that 5-8 minutes typically elapse between the emergency call and ambulance arrival, and 8-12 minutes until the first shock is delivered. Achieving defibrillation within the optimal early time window is feasible through public-access AED deployment: AEDs should be placed in high-traffic public locations and public buildings, particularly at sites where at least one resuscitation is expected to occur every five years. AEDs guide lay rescuers with voice prompts during BLS, perform rhythm analysis approximately every two minutes, and -when a shockable rhythm is detected - facilitate defibrillation. (20 - 22, 55, 59 - 61)

1.7.2. Advanced life support

Advanced Life Support can be defined as a life-saving protocol that extends ongoing BLS through the use of invasive techniques, pharmacological therapy, and trained healthcare personnel. During ALS, the objectives are to provide further circulatory and ventilatory support, correct hemodynamic instability, and ensure rapid transfer to an appropriately equipped treatment facility (e.g., cardiac catheterization laboratory, emergency or intensive care unit) in order to maximize survival and achieve the best possible neurological outcome.

The 2025 ERC reinforces that earlier initiation of ALS interventions remains central to improving outcomes from both IHCA and OHCA. Compared with prior iterations, the document places stronger emphasis on ensuring effective oxygenation and ventilation, optimising defibrillation delivery, and using physiological monitoring to guide resuscitation when available. (56)

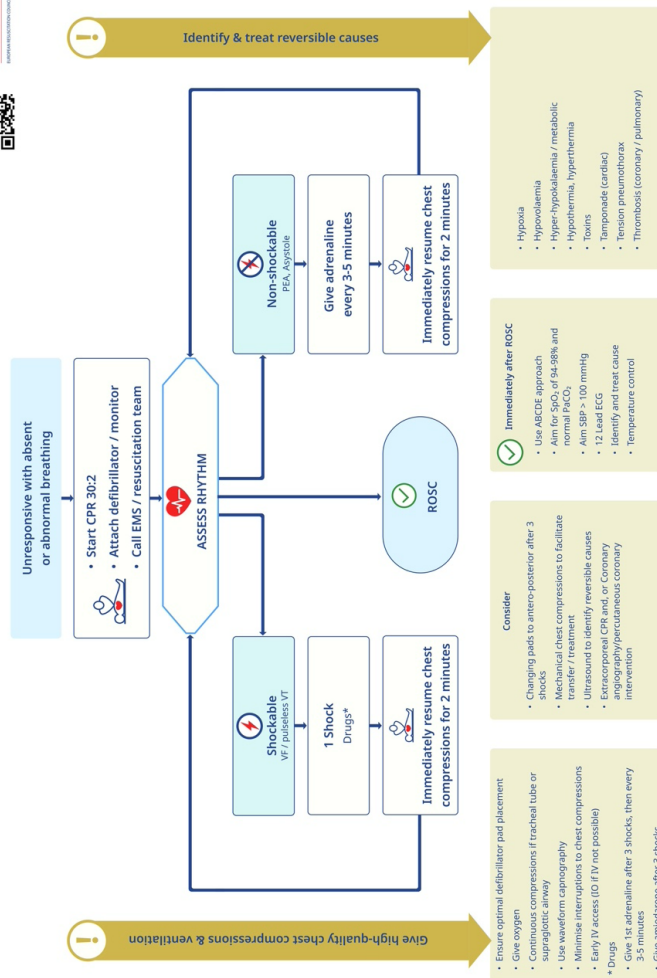


Figure 3. Advanced life support algorithm (56) Available from: <https://www.erc.eu/science-research/guidelines/guidelines-2025-english/>

The ALS algorithm remains the familiar three-branch structure (based on initial, shockable vs. non-shockable rhythms and ROSC), built around uninterrupted 2 minute CPR cycles with rapid rhythm checks and early reversible-cause management (Figure 3.). Key steps include: immediate recognition, call for help, initiation of CPR, attachment of defibrillator/monitor, and rhythm assessment at brief, structured intervals. (56)

For shockable rhythms (VF/VT), the algorithm prioritises immediate defibrillation with minimal interruption to compressions, followed by 2-minute CPR cycles, rhythm reassessment, and escalation of therapy (including adrenaline and amiodarone administration after repeated shocks) while actively addressing reversible causes. For non-shockable rhythms (PEA/asystole), the algorithm emphasises early adrenaline, high-quality CPR, airway/ventilation optimisation, and systematic search for reversible causes, with rhythm reassessment at regular intervals. Post-ROSC care is integrated as an essential continuation of ALS, including stabilisation of airway/breathing/circulation and transition to structured post-cardiac arrest management. (56)

1.7.3. Post cardiac arrest management

Post-cardiac arrest syndrome (PCAS) refers to the clinical entity that develops after ROSC. By definition, PCAS is a constellation of manifestations driven primarily by global, multi-organ ischemia-reperfusion injury following resuscitation; consequently, affected patients frequently require complex intensive care (Figure 4.). The goals of management are to restore and maintain effective circulation - including a stable cardiac rhythm and adequate tissue perfusion - preserve central nervous system function, and ultimately optimize quality of life. (62)

Management of PCAS begins with the ROSC; however, to maximize survival and achieve the best possible neurological outcome, patients should be transported to specialized cardiac intensive care units or cardiac arrest centers (CACs) for ongoing treatment. Both short- and long-term survival after resuscitation are substantially influenced by patient age, known or previously unrecognized comorbidities, the initial rhythm, the duration of circulatory collapse (no-flow time), and the duration of cardiopulmonary resuscitation (low-flow time). Long-term outcome in successfully resuscitated patients is largely determined by post-resuscitation neurological status, which reflects the extent of

underlying ischemia–reperfusion injury and is further modulated by stress hormones, heat-shock proteins, and complement system overactivation. (62, 63, 64)

Target-organ hypoperfusion results from the no-flow and low-flow phases before and during resuscitation and, after ROSC, may manifest as neurological, cardiovascular, pulmonary, renal, and metabolic dysfunction; in severe cases, a “systemic inflammatory response syndrome (SIRS)-like” syndrome may develop. The overarching objectives of PCAS care are to prevent recurrent arrhythmias, stabilize hemodynamic, normalize target-organ perfusion, and minimize cellular and neurological injury. Management therefore requires both etiologic treatment of the precipitating cause of arrest and supportive measures, including hemodynamic support, maintenance of cerebral perfusion, continuous monitoring of vital parameters, and pharmacological neuroprotection. (62, 63, 64)



Figure 4. Set up of post cardiac arrest management in the cardiac intensive care unit.

The ERC–ESICM 2025 post-resuscitation care guideline refines temperature management, post-ROSC rhythm control, and pharmacotherapy to reduce secondary brain injury while avoiding interventions without proven benefit.

The guideline shifts emphasis from “targeted temperature management” terminology to “active temperature control”, with a primary focus on fever prevention in comatose survivors. It recommends actively targeting $\leq 37.5^{\circ}\text{C}$ and maintaining fever prevention for 36–72 h after ROSC. Importantly, comatose patients who are mildly hypothermic (32–

36 °C) after ROSC should not be actively rewarmed to normothermia. When temperature control devices are used (surface or endovascular), systems with continuous monitoring and feedback are preferred to maintain the target reliably.

A dedicated section addresses recurrent and refractory post-ROSC arrhythmias: management should follow the ERC ALS peri-arrest algorithms, while simultaneously treating reversible triggers (e.g., coronary occlusion, electrolyte disturbances, 4H/4T).

Pharmacotherapy is framed around targeted indications rather than routine use. The guideline recommends levetiracetam or sodium valproate, as first-line antiepileptics (in addition to sedatives) for post-arrest seizures, and advises against seizure prophylaxis. It also states there is insufficient evidence for any specific neuroprotective drug to improve neurological outcome, and explicitly recommends not giving steroids routinely after cardiac arrest. (62)

1.8. Survival after successful resuscitation

Survival and neurological outcomes after OHCA vary markedly across countries. Survival to hospital discharge (or 30-day survival) ranges from 3.4% to 15.6%. (65) Even within the same region or country - and under a similar healthcare system - outcomes can differ substantially, reflecting variations in population demographics and community response (e.g., bystander CPR and defibrillation), which may also evolve over time. (66-67) In many settings, particularly where emergency care systems are still developing, resuscitation outcomes are not routinely measured or reported in standardized way.

In Europe, the EuReCa registries has conducted 3-month cross-sectional surveys across approximately 30 countries. Across these surveys, the mean reported rate of survival to hospital discharge declined from 10.3% in 2014 (range 1.1-30.8%) to 8.0% in 2017 (range 0-18%) and 7.5% in 2022 (range 3.1-35%). (20 - 22)

1.9. Prognostic tools after return of spontaneous circulation

Multimodal prognostication is a central principle of post-cardiac arrest care, aiming to provide accurate outcome prediction while minimizing the risk of premature withdrawal of life-sustaining treatment. Current ERC guidelines emphasize that no single parameter is sufficiently reliable when used in isolation; instead, neurological prognosis should be based on a structured combination of clinical examination, biomarkers, neuroimaging, and electrophysiological assessments (see Figure 5.). (62)

Clinical evaluation remains fundamental and includes assessment of pupillary and corneal reflexes, motor response, and the presence of myoclonus after sedation has been cleared. Biomarkers provide supportive information regarding the extent of hypoxic–ischemic brain injury when interpreted in serial measurements. Neuroimaging can reveal diffuse cerebral oedema or ischemic morphology changes associated with poor outcome. Electrophysiological tools offer additional objective markers of severe neurological damage. (62) (see Figure 5.)

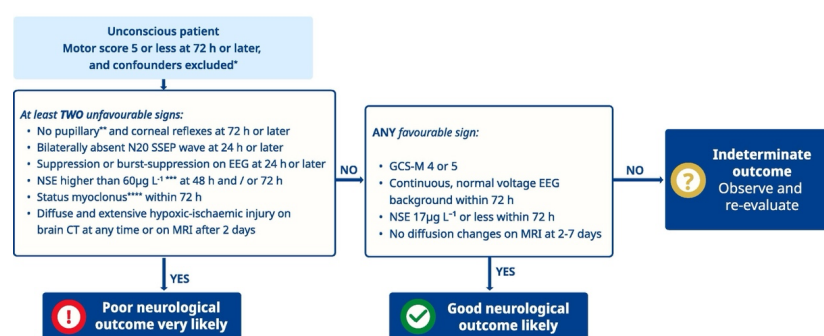


Figure 5. Algorithm for neurological prognostication in patients who remains comatose after cardiac arrest. (62) *CT: computer tomography, EEG: electroencephalography, GCS-M: Glasgow Coma Scale motor score, NSE: neuron specific enolase, SSEP: somatosensory evoked potential. Available from: <https://www.erc.edu/science-research/guidelines/guidelines-2025/guidelines-2025-english/>.*

Multiple prognostic scoring systems (PSS) have been proposed to estimate neurological outcome and mortality after OHCA. However, these tools vary substantially in included predictors, reported performance, and the characteristics of the resuscitated populations in which they were developed and validated, limiting cross-study comparability. To date, only a limited number of scores appear sufficiently practical and robust to support early neurological or mortality prognostication during the initial intensive care period after admission. If prognostic scores are to inform clinical decision-making, the key requirement is the ability to identify poor outcome with near-perfect specificity (approximately 100%), thereby minimizing the risk of premature withdrawal of care in patients with delayed recovery. (68, 69)

At present, there is no consensus regarding which scoring system can be applied safely as a bedside decision-support tool in routine practice.

1.10. Decision making and potential withdrawal of life sustaining treatment

The duration of post-resuscitation intensive care ranges from a few hours to several weeks, depending on the required level of organ support and the recovery of target-organ function. Neurological status - reflecting both structural and functional integrity of the central nervous system - is the principal determinant of survival. Prolonged intensive care unit (ICU) treatment imposes substantial burdens on healthcare systems, with the highest associated costs (approximately €120,000-168,000 for patients with a good one-year neurological outcome) and considerable consumption of human and material resources, while also generating profound psychological distress for patients' relatives. (62, 70)

Against a background of evolving medical practice and societal expectations, clinicians are increasingly challenged to provide families with objective, timely information regarding prognosis. A central difficulty is identifying those patients who are likely to survive with meaningful neurological recovery. Approximately 66% of patients admitted to the ICU after OHCA die in hospital as a consequence of hypoxic-ischemic brain injury. Notably, many deaths occur following withdrawal of life-sustaining treatment (WLST) when a poor neurological outcome is anticipated. Therefore, accurate prognostication is essential to avoid premature or inappropriate WLST first, than to prevent the deployment of intensive, costly resources in situations where recovery is unlikely. (71, 72)

Decisions regarding WLST are inherently complex and require shared deliberation between the treating team and the patient's relatives, often influenced by emotional, cultural, and religious considerations. Prognostication is further complicated - and frequently delayed - by targeted temperature management, prolonged sedation, and the use of neuromuscular blockade, all of which can obscure neurological assessment. Under current Hungarian law, neither active nor passive euthanasia is permitted.

Current guidelines recommend a multimodal approach to post-cardiac arrest prognostication, integrating clinical examination with biomarkers, neuroimaging, and electrophysiological testing. (62, 73)

2. Objectives

The overarching objective of this topic is to evaluate post-resuscitation intensive care strategies and care pathways in relation to outcome variability, and to identify, quantify, and validate prognostic and age related factors that can support evidence-based escalation/de-escalation decisions and resource allocation in patients requiring cardiopulmonary resuscitation.

2.1 Prediction performance of scoring systems after OHCA

The objectives are to synthesize and compare the predictive performance of established post-OHCA scoring systems for neurological outcome and mortality, emphasizing discrimination and calibration where available, and to determine which tools best support real-world decision-making. A further objective is to translate these findings into an implementable ICU workflow for early risk stratification that complements guideline-consistent, multimodal prognostication rather than replacing it.

2.2 Age-treatment interactions in OHCA

The objectives are to describe age-stratified outcome patterns, identify independent predictors of survival such as initial shockable rhythm (VF/VT), witnessed status, and defibrillation/AED use, and test whether age modifies the effect of key resuscitation interventions or predictors. Finally, the work aims to develop and internally validate a prediction approach suitable for prehospital and early in-hospital decision support, and to outline implications for geriatric-tailored resuscitation and post-resuscitation care pathways.

3. Methods

All studies included in this dissertation were performed in compliance with the Declaration of Helsinki and in accordance with relevant Hungarian laws and regulations.

3.1 Study design and statistics for prediction performance of scoring systems after out-of-hospital cardiac arrest (systematic review and meta-analysis)

We conducted and reported this systematic review and meta-analysis in accordance with the PRISMA 2020 statement and the Cochrane Handbook recommendations. (74, 75) The protocol was registered in PROSPERO (CRD42021284545). (76)

3.1.1. Eligibility criteria

The research question was defined using the Population, Intervention, Comparator, and Outcomes (PICO) framework. We included cohort studies and clinical trials, while excluding case reports, case series, conference abstracts, and publications without original data. The target population comprised successfully resuscitated adult patients after OHCA. Eligible studies evaluated prognostic scoring systems or prediction models intended to estimate clinical outcomes using readily available parameters after ICU admission. Studies based on mixed OHCA/IHCA populations were excluded.

The primary endpoint was post-resuscitation neurological status, classified by the Cerebral Performance Category (CPC) as good (CPC 1-2) or poor (CPC 3-5), consistent with standard ICU practice. (77, 78) Secondary endpoints included mortality at predefined time points following cardiac arrest.

3.1.2. Information sources, search strategy, and study selection

A systematic search was performed on April 24, 2023, in four databases: MEDLINE (via PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus. Two reviewers independently screened records using reference-management software (EndNote X9.3.3; Clarivate Analytics, 2020). Duplicates were removed both automatically and manually. Discrepancies were adjudicated by a third reviewer.

Studies were eligible for meta-analysis if (i) OHCA patients were enrolled consecutively, (ii) prediction scores were used to estimate neurological outcome and/or mortality, and (iii) diagnostic accuracy data were reported (sensitivity/specificity; counts of true

positives (TP), false negatives (FN), false positives (FP), true negatives (TN); and/or area under curve (AUC) with confidence intervals (CI)). Only full-text publications were included in the qualitative synthesis and quantitative meta-analysis.

3.1.3. Data collection and data items

Two authors independently extracted data using a standardized form (Microsoft Excel for Mac; Microsoft, 2022). A third reviewer verified data accuracy. From each study we extracted: title, first author, publication year, digital object identifier (DOI), study setting, study period, design, recruitment period, and population characteristics (sex distribution, age, initial rhythm). We also collected information on targeted temperature management (TTM), admission laboratory values (lactate, creatinine, pH), resuscitation time intervals (no-flow and low-flow), and the variables included in each prediction model/score. For diagnostic performance, we recorded sensitivity and specificity across thresholds, TP/FN/ FP/ TN counts, AUC with CI, cut-off values, and the clinical endpoints assessed.

3.1.4. Risk of bias assessment

Risk of bias and applicability were evaluated using PROBAST (Prediction model Risk Of Bias ASsessment Tool), in line with Cochrane guidance. (79) Two reviewers assessed studies independently, resolving disagreements by consensus.

3.1.5. Synthesis methods

Analyses were performed using R (version 4.1.2) and the R script associated with Freeman's online tool. (80) Statistical significance was set at $p < 0.05$.

For each score–outcome pair, AUC values and CIs were extracted; meta-analysis was undertaken when at least three relevant cohorts were available. Standard deviations were derived from CIs, and where CIs were unavailable, the method of Hanley et al. was applied. (81) Because some studies reported multiple prognostic scores, we accounted for within-study correlations using a multivariable meta-analytic model (rma.mv in the metafor package), with robust variance estimation using the Pustejovsky correction (coef_test in the clubSandwich package). (82) Sensitivity analyses under varying within- and between-study correlation assumptions yielded materially similar pooled AUC estimates and p-values. For remaining AUC syntheses, we used a univariate inverse-variance random-effects model fitted by restricted maximum likelihood. Heterogeneity was quantified using I^2 (with CI) and the Cochrane Q test; I^2 thresholds were interpreted

as 25% (low), 50% (moderate), and 75% (high) heterogeneity. (74) Discriminatory performance by AUC was categorized as excellent (≥ 0.9), good (0.8–0.9), fair (0.7–0.8), poor (0.6–0.7), and fail (0.5–0.6). (83, 84) To further characterize the diagnostic performance of the Cardiac Arrest Hospital Prognosis (CAHP) and OHCA scores, we extracted the numbers of patients with CPC 1–2 and CPC 3–5, along with sensitivity and specificity at reported thresholds, and reconstructed 2×2 tables (TP/FP/FN/TN) for each threshold. To model the dependence between sensitivity and specificity across thresholds within studies, we generated Summary Receiver Operating Characteristic (SROC) curves with CIs using the Steinhauser and Rücker method, which accommodates correlated contingency tables arising from multiple thresholds in the same study; this approach requires known threshold values and includes many parameters. (85) In addition, we fitted SROC curves using the non-Bayesian Rutter and Gatsonis approach by randomly selecting one threshold per study (ensuring meaningful separation among selected thresholds), repeating this procedure 16 times. (86)

Based on Harbord’s work, the Rutter and Gatsonis method is mathematically equivalent to the bivariate Reitsma/Chu model for pooled sensitivity and specificity. (86, 87, 88) Because pooled sensitivity and specificity are interpretable only when based on a common threshold, we calculated pooled estimates for thresholds 200 and 150 for CAHP and 60 and 40 for the OHCA score, and displayed these on ROC plots.

When individual-level or otherwise sufficiently granular data were available, we additionally derived outcome measures not explicitly reported in the original publications, such as sensitivity and specificity across multiple alternative thresholds.

3.2. Study design and statistics for age–treatment interactions in OHCA

3.2.1. Study design and setting

We performed a retrospective cohort study based on the registry of the HNAS, including all OHCA events recorded between 1 November 2018 and 28 February 2025. The centralized HNAS system ensures nationwide coverage through standardized operating procedures and mandatory reporting, resulting in minimal data attrition. The study was approved by the Hungarian National Ethics Committee, which authorized the collection and analysis of OHCA-related data for this observational evaluation of OHCA epidemiology, regional variation, and mortality in Hungary (Reference Nos.: IV/3043/2021/EKU and IV/3043-3/2021/EKU).

3.2.2. Study population and data selection

Between 1 November 2018 and 28 February 2025, HNAS registered 200,367 cases. We excluded 6,126 events attributable to non-medical aetiologies (including trauma, drowning, electrocution, and gynaecological causes) and 17,839 cases involving paediatric patients (<18 years) or missing age information. An additional 28,440 cases were removed because resuscitation was not attempted by EMS personnel or because essential clinical variables were incomplete. The final analytic cohort therefore comprised 147,962 adult OHCA cases in which resuscitation was attempted (see Figure 6.).

3.2.3. Age stratification and variable definitions

Patients were stratified at 65 years, in line with common geriatric definitions and prior OHCA literature. (89) Age was evaluated both continuously and categorically (elderly: ≥ 65 years; non-elderly: <65 years). Collected clinical variables included initial rhythm (VT, VF, PEA, asystole, bradycardia), witness status (medical personnel, non-medical bystander, unwitnessed), arrest location (home, public, other), and sex. Recorded HNAS interventions comprised shock delivery (via AED or manual defibrillation), use of mechanical chest compression, and EMS response times. We analysed AED availability separately from shock delivery, recognizing that device presence does not imply clinical use.

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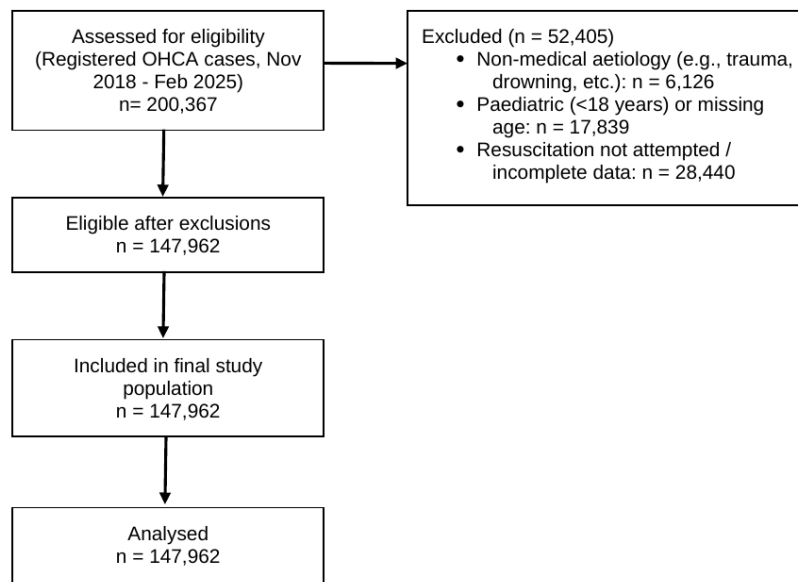


Figure 6. Flowchart of study population selection.

3.2.4. Statistical analysis

Baseline characteristics were compared between elderly and non-elderly groups using chi-square tests for categorical variables and t-tests for continuous variables. Associations with survival were examined using logistic regression, reported as odds ratios (ORs) with 95% confidence intervals (CIs). A final multivariable logistic regression model was constructed using clinically relevant predictors, selected based on clinical rationale and statistical significance ($p < 0.05$). Discrimination was assessed using the area under the receiver operating characteristic curve (AUC), while calibration was evaluated with the Brier score and calibration plots. Clinical utility was further explored through number needed to treat (NNT) estimates. NNT was calculated as the reciprocal of the unadjusted absolute risk difference. Adjusted absolute risk difference (ARD) and potential impact fraction (PIF) were obtained by model-based standardisation: survival probabilities were predicted for every patient with the exposure set to 1 and to 0 (other covariates as observed; for witness status, the reference was ‘no witness’) and averaged. $ARD = \text{mean predicted survival if exposed} - \text{if unexposed}$; $PIF = (\text{mean predicted survival under$

universal exposure – observed survival) / observed survival. 95% CIs were obtained from 2,000 bootstrap resamples with model re-estimation. Analyses were performed in Python 3.8 (Python Software Foundation, USA) using the statsmodels and scikit-learn libraries, with statistical significance defined as $p < 0.05$.

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3.2.5. Age-specific treatment effectiveness

To assess whether treatment effects varied by age, we incorporated age×treatment interaction terms. Interactions were tested for (1) sex×age, (2) initial rhythm×age, and (3) shock delivery×age. Only interactions remaining significant ($p < 0.05$) after correction for multiple testing were reported. For significant interactions, age-stratified effect estimates with CIs were calculated, and results are presented both as interaction ORs (reflecting the change in treatment effect with age) and as clinically interpretable treatment effects in elderly versus non-elderly patients.

4. Results

4.1. Results of prediction performance of scoring systems after out-of-hospital cardiac arrest (systematic review and meta-analysis)

4.1.1. Search and selection

The systematic search resulted in 27,479 records across four databases. Following automated and manual removal of duplicates, 15,707 records underwent personal screening. Overall, 51 full-text articles were included in the qualitative synthesis, of which 24 were eligible for inclusion in the quantitative meta-analysis (Figure 7.).

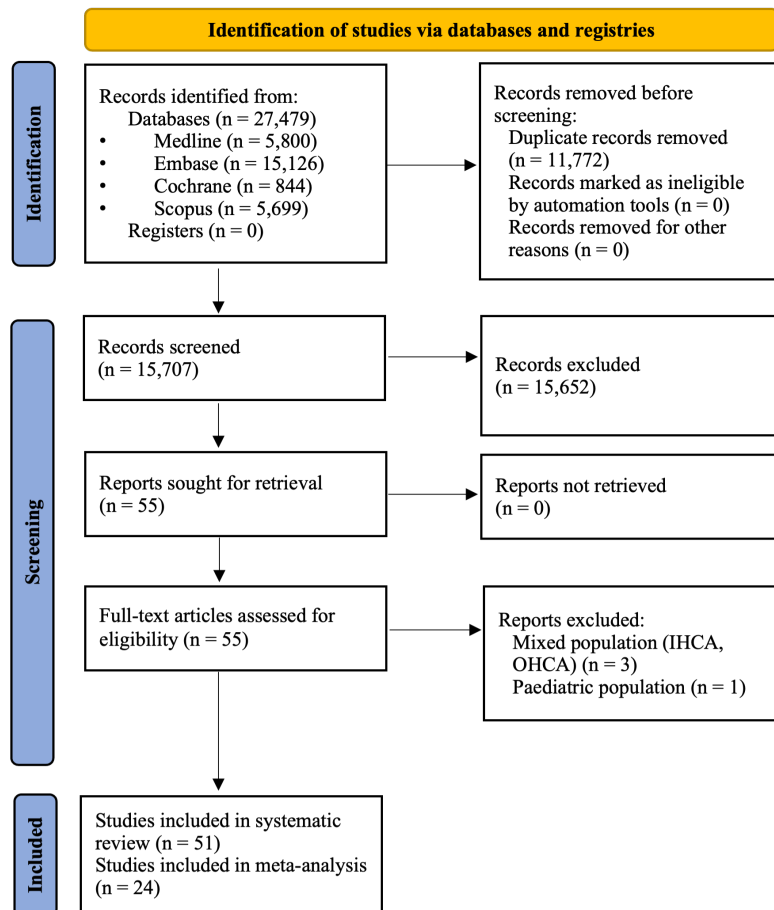


Figure 7. PRISMA 2020 flowchart representing the study selection process.

4.1.2. Systematic review

We identified 51 articles and data of 86,321 patients data were used to develop and validate 36 prediction scoring systems (PSS) or models. (90-140)

These scoring systems were developed and validated mainly in Asian or Caucasian populations, no data from Latin American or African populations. Across studies, the sex distribution varied markedly (male 56-88% of participants). The use of therapeutic hypothermia or targeted temperature management as part of post-resuscitation ICU care also differed substantially between cohorts, ranging from 4% to 100%. In 33 of the 51 included articles, patient enrolment and data collection commenced before 2013. Within the systematic review, we checked all the predictors included into each PSS. The number of variables per score ranged from 1 to 18, with a median of six. Initial rhythm was the most frequently included predictor (25 PSS), followed by age (18 PSS), no-flow time (14 PSS), low-flow time (13 PSS), admission pH (13 PSS), and witnessed status (12 PSS).

4.1.3 Basic characteristics of studies included in the meta-analysis

Basic characteristics of the 24 studies included in the meta-analysis are summarized in Tables 2 and 3. (90, 91, 93, 96, 97, 100, 102, 105, 106, 110–112, 118-121, 127, 129, 130, 132, 133, 136, 137, 140) Collectively, these cohorts contain data of 13,261 OHCA patients. Seven prognostic scores were eligible to include in quantitative synthesis: CAHP, C-GRaPH, NULL-PLEASE, OHCA, rCAST, SOFA, and TTM (see details about the scores in Table 2). The most frequently reported endpoint was neurological outcome at hospital discharge (Table 3).

The studies were conducted across 15 countries between 1999-2022. Baseline cohort characteristics were highly heterogeneous, including broad ranges in age (53-81 years), sex distribution (male 56-82%), proportion of shockable initial rhythms (8-89%), no-flow time (0-10 minutes) and low-flow time (15-30 minutes), and admission laboratory values (lactate 3.6-11.0 mmol/L; pH 6.97-7.36; creatinine 88-202 µmol/L). Use of targeted temperature management also varied substantially (11-100%). See in Table 4.

4.1.4. Risk of bias assessment

Study quality was evaluated using the PROBAST checklist. Across both ROB and applicability assessments, most domains were predominantly classified as low risk/low concern.

Score	Predicted outcome	Intended population	When it can be calculated	Variables included	Practical strengths	Important limitations
CAHP (121)	Neurological outcome	OHCA survivors	At hospital or ICU admission	Age; initial non-shockable rhythm; time from collapse to basic life support; time from basic life support to ROSC; arrest location; epinephrine dose; arterial pH	Widely studied; uses routinely available variables, provides low-, intermediate- and high-risk categories	Requires reliable time-interval data and epinephrine dose; relatively complex calculation
C-GRaPH (111)	Neurological outcome	OHCA survivors with TTM	At hospital or ICU admission	Coronary artery disease; glucose, initial rhythm, age, arterial pH	Very simple bedside score; only five equally weighted variables; total score 0–5	Developed in a selected TTM population; omits no-flow and low-flow times
NULL-PLEASE (100)	In-hospital mortality	OHCA survivors	At hospital or ICU admission	Initial rhythm; unwitnessed arrest; no-flow and low-flow times, pH, serum lactate, end-stage renal failure, age, ongoing resuscitation, extracardiac cause	Memorable acronym; fast; applicable even before ROSC in some cases; useful for mortality discussions	Primarily predicts mortality rather than neurological recovery; performance depends on accurate resuscitation times
OHCA (90)	Neurological outcome	OHCA survivors	At hospital or ICU admission	Initial rhythm; estimated no-flow time; estimated low-flow interval; blood lactate; blood creatinine	Compact, cardiac-arrest-specific model; uses five admission variables	Continuous weighted formula is less convenient at the bedside; time intervals may be uncertain; derived from older cohorts
rCAST (96)	Neurological outcome	OHCA survivors with TTM	At hospital or ICU admission	Initial rhythm; witnessed status and time to ROSC; arterial pH; lactate; Glasgow Coma Scale motor score	Uses five available variables; designed for rapid emergency-department use; provides severity groups: low ≤ 5.5 , moderate 6.0–14.0, high ≥ 14.5	Originally designed for TTM-treated OHCA cohorts; applicability to in-hospital arrest and other settings requires caution; neurological examination may be confounded early after ROSC
SOFA (120)	ICU mortality	General adult ICU population	At hospital or ICU admission	Six organ systems: neurological, respiratory, cardiovascular, hepatic, renal and coagulation	Well-known ICU score; useful for monitoring evolution of multiorgan failure; permits serial comparison	Not cardiac-arrest-specific
TTM (110)	Neurological outcome	OHCA survivors with TTM	At ICU admission	Age, location of OHCA, initial rhythm no-flow and low-flow times; epinephrine administration; absent corneal and pupillary reflexes; GCS motor response pH; arterial PaCO ₂	Integrates pre-hospital events, early neurological examination and laboratory data; useful for structured risk stratification	Difficult to calculate score; early brainstem reflexes and GCS may be confounded; derived from a selected clinical-trial population; external validation showed imperfect discrimination

Table 2. Comparison of prediction scores included to the meta-analysis

Table 3. Basic characteristics of studies included in the meta-analysis. *Parameters expressed as mean with standard deviation (*), or median with interquartile range (**) as appropriate. dev: development cohort, N/A: not available, val: validation cohort.*

First author, year	Study type	Study design	Study period	Investigated score systems	No of pts (N)	Male (%)	Age (year)
Adrie et al.,(90) 2006 (dev)	multicentre	prospective	1999-2003	OHCA	130	72	55 (47–69)**
Adrie et al.,(90) 2006 (val)	multicentre	prospective	2003-2005	OHCA	210	80	56 (45–69)**
Bae et al., (91) 2021	single-centre	retrospective	2014-2016	CAHP, C-GRaPH, OHCA	671	68	63 (52–74)**
Blatter et al., (93) 2023	single-centre	prospective	2012-2022	CAHP, OHCA,	687	72	66 (56–76)**
Chen et al., (96) 2022	single-centre	retrospective	2015-2021	rCAST	108	61	66 (56–78)**
Choi et al.,(97) 2018	single-centre	retrospective	2010-2013	OHCA, SOFA	173	69	53 (±15)*
Gue et al.,(100) 2020 (dev)	multicentre	retrospective	2015-2018	NULL-PLEASE	300	71	N/A
Gue et al.,(100) 2020 (val)	multicentre	prospective	2015-2018	NULL-PLEASE	400	75	N/A
Heo et al., (102) 2022	multicentre	retrospective	2015-2018	CAHP, C-GRaPH, NULL-PLEASE, OHCA, rCAST, TTM	1186	71	58 (47–70)**
Hunziker et al.,(105) 2011	multicentre	retrospective	2006-2008	OHCA	128	69	62 (52–77)**
Isenschmid et al.,(106) 2019	single-centre	prospective	2012-2017	CAHP, OHCA	349	73	65 (56–75)**
Kägi et al., (110) 2020	single-centre	retrospective	2016	TTM	100	N/A	N/A
Kiehl et al.,(111) 2017 (dev)	multicentre	prospective	2008-2012	C-GRaPH	122	68	60 (±16)*
Kiehl et al.,(111) 2017 (val)	multicentre	prospective	2012-2014	C-GRaPH	344	56	62 (±15)*
Kim et al.,(112) 2020	single-centre	retrospective	2009-2017	CAHP, C-GRaPH, OHCA	311	71	55 (44–69)**
Leusher et al., (118) 2019	single-centre	prospective	2012-2017	CAHP, OHCA	336	72	64 (±14)*
Martinell et al., (119) 2017	RCT	multicentre	2010-2013	CAHP, OHCA, TTM	933	81	65 (57–73)**
Matsuda et al.,(120) 2020	single-centre	retrospective	2015-2018	SOFA	231	76	61 (±17)*
Maupain et al.,(121) 2016 (dev)	multicentre	prospective	2011-2012	CAHP	819	69	62 (±15)*
Maupain et al.,(121) 2016 (val.1)	multicentre	retrospective	2007-2010	CAHP	367	71	62 (±15)*
Maupain et al.,(121) 2016 (val.2)	multicentre	prospective	2013-2014	CAHP	1,129	67	62 (±16)*
Pareek et al. (127) 2020 (dev)	multicentre	retrospective	2012-2017	CAHP, OHCA, TTM	373	74	64 (52–75)**
Pareek et al. (127) 2020 (val.1)	single-centre	retrospective	2013-2017	CAHP, OHCA	325	82	64 (55–73)**
Pareek et al. (127) 2020 (val.2)	single-centre	retrospective	2016-2018	CAHP, OHCA	148	76	64 (54–74)**
Pham et al.,(129) 2021	single-centre	prospective	2009-2019	CAHP, NULL-PLEASE, OHCA	386	79	61 (±12)*
Sauneuf et al.,(130) 2020	multicentre	retrospective	2009-2016	CAHP	176	72	81 (79–84)**
Shibahashi et al., (132) 2020	multicentre	retrospective	2012-2013	CAHP, OHCA	2468	68	70 (60–80)**
Tuchida et al. (133) 2021	multicentre	retrospective	2015-2018	CAHP, NULL-PLEASE, OHCA, rCAST	189	59	N/A
Vedamurthy et al., (136) 2021	single-centre	retrospective	2016-2019	CAHP	158	73	66 (±13)*
Wu et al., (137) 2022	single-centre	retrospective	2015-2019	CAHP	197	61	N/A
Yoon et al.,(140) 2018	single-centre	retrospective	2010-2015	SOFA	143	66	61 (48–72)**

Table 4. Basic characteristics of post-cardiac-arrest patients in studies included in the meta-analysis. *Parameters expressed as mean with standard deviation (*), or median with interquartile range (**)* as appropriate. dev: development cohort, N/A: not available, TTM: targeted temperature management, val: validation cohort.

First author, year	Shockable initial rhythm (%)	No-flow time (min)	Low-flow time (min)	Serum lactate (mmol/L) †	pH †	TTM (%)
Adrie et al.,(90) 2006 (dev)	42	6 (3–10)**	15 (10–25)**	6.7 (3.7–11.0)**	7.25 (7.15–7.34)**	11
Adrie et al.,(90) 2006 (val)	38	7 (3–10)**	20 (12–33)**	6.2 (3.2–11.3)**	N/A	74
Bae et al., (91) 2021	30	2 (1–5)**	20 (10–32)**	8.7 (5.5–13.1)**	7.16 (6.99–7.32)**	52
Blatter et al., (93) 2023	53	0 (0–5)**	15 (10–25)**	5.6 (2.9–9.0)**	7.25 (7.12–7.33)**	51
Chen et al., (96) 2022	28	N/A	28 (15–41)**	6.2 (4.3–9.6)**	7.36 (7.26–7.43)**	100
Choi et al.,(97) 2018	34	6 (2–11)**	22 (16–33)**	7.9 (5.8–10.5)**	7.29 (7.21–7.36)**	100
Gue et al.,(100) 2020 (dev)	89	N/A	N/A	N/A	N/A	N/A
Gue et al.,(100) 2020 (val)	63	N/A	N/A	N/A	N/A	N/A
Heo et al., (102) 2022	36	1 (0–6)**	25 (14–38)**	9.1 (4.3–12.6)**	7.11 (6.95–7.25)**	100
Hunziker et al.,(105) 2011	23	4 (1–6)**	20 (10–27)**	9.7 (4.3–14.6)**	N/A	34
Isenschmid et al.,(106) 2019	55	0 (0–8)**	15 (10–15)**	6.6 (4.6–9.7)**	7.26 (7.19–7.33)**	57
Kägi et al., (110) 2020	34	N/A	N/A	N/A	N/A	100
Kiehl et al.,(111) 2017 (dev)	67	N/A	30 (±17)*	N/A	7.17 (± 0.15)*	100
Kiehl et al.,(111) 2017 (val)	38	N/A	27 (± 7)*	N/A	7.15 (± 0.19)*	100
Kim et al.,(112) 2020	37	5 (0–10)**	25 (14–35)**	10.0 (5.0–14.2)**	7.13 (6.91–7.28)**	100
Leusher et al., (118) 2019	56	4 (±6)*	19 (±15)*	N/A	N/A	100
Martinelli et al., (119) 2017	78	N/A	N/A	N/A	N/A	N/A
Matsuda et al.,(120) 2020	68	N/A	N/A	11.0 (± 5.15)*	7.07 (6.89–7.26)**	62
Maupain et al.,(121) 2016 (dev)	44	5 (±6)*	23 (±15)*	N/A	7.19 (±0.18)*	N/A
Maupain et al.,(121) 2016 (val.1)	54	5 (±6)*	19 (±14)*	N/A	7.21 (±0.16)*	N/A
Maupain et al.,(121) 2016 (val.2)	54	5 (±6)*	22 (±14)*	N/A	7.18 (±0.18)*	N/A
Pareek et al. (127) 2020 (dev)	70	2 (0–7)**	25 (17–38)**	4.9 (2.4–8.9)**	7.21 (7.08–7.30)**	N/A
Pareek et al. (127) 2020 (val.1)	82	N/A	N/A	3.60 (1.9 – 7.4)**	7.27 (7.17 -7.34)**	N/A
Pareek et al. (127) 2020 (val.2)	78	N/A	N/A	4.93 (2.8 – 8.4)**	7.24 (7.07 – 7.35)**	N/A
Pham et al.,(129) 2021	82	4 (±5)*	19 (±13)*	4.8 (±4.4)*	7.24 (±0.13)*	90
Sauneuf et al.,(130) 2020	39	5 (2–10)**	20 (13–27)**	4.5 (2.5–8.5)**	7.30 (7.20–7.39)**	45
Shibahashi et al., (132) 2020	22	10 (4–14)**	30 (16–41)**	N/A	6.97 (6.84–7.13)**	N/A
Tuchida et. al. (133) 2021	28	N/A	N/A	N/A	N/A	53
Vedamurthy et al., (136) 2021	N/A	N/A	N/A	7.7 (±4.1)*	N/A	N/A
Wu et al., (137) 2022	8	N/A	N/A	N/A	N/A	N/A
Yoon et al.,(140) 2018	25	N/A	N/A	N/A	N/A	100

4.1.5. Performance of scores to predict neurological outcome at hospital discharge

Among the 24 included studies, 14 assessed neurological outcome at hospital discharge. (90, 91, 93, 102, 104, 106, 111, 112, 118, 121, 127, 130, 136, 138) Sufficient data were available for three prognostic scores (CAHP, C-GRaPH, OHCA) to pool AUCs from ROC analyses. Across studies, neurological outcome was reported using the CPC and higher AUC values indicated better discrimination for poor neurological outcome.

The CAHP score demonstrated the highest pooled AUC (0.876; 95% CI, 0.853-0.898), whereas C-GRaPH showed the lowest (0.764; 95% CI, 0.738-0.791). Substantial heterogeneity was observed for CAHP ($I^2 = 90\%$). We found significant difference with a priority in performance of CAHP in comparison with OHCA and C-GRaPH scores. Forest plots are presented in Figure 8.

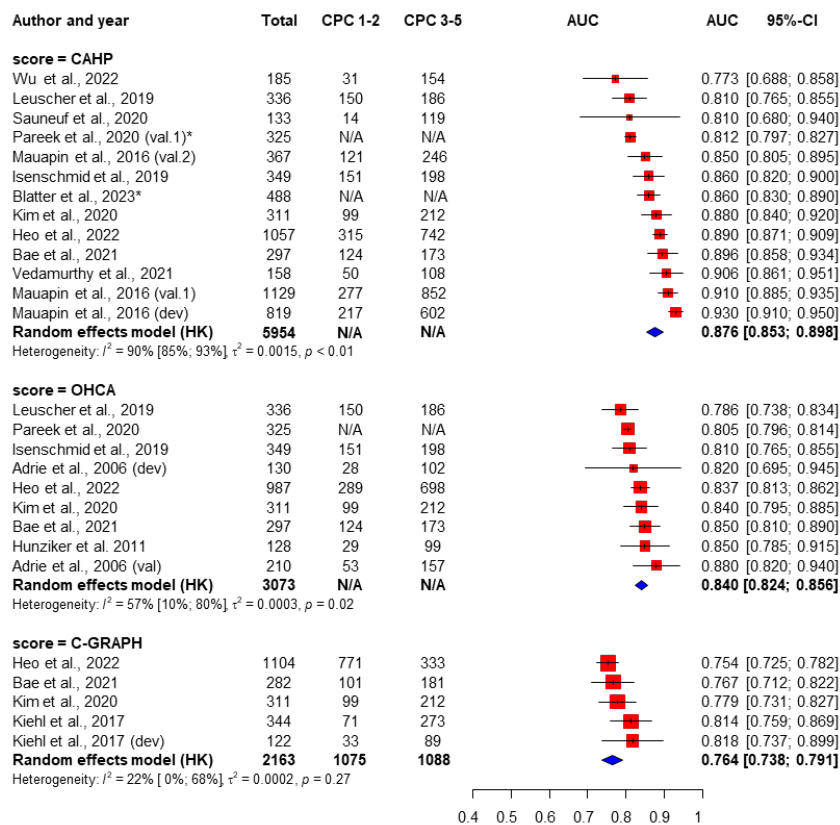


Figure 8. Random-effects pooled AUC of ROC curves and heterogeneity test for CAHP, OHCA and C-GRaP scores predicting neurological outcome at hospital discharge. *AUC: area under curve, CI: confidence interval, CPC: cerebral performance category, dev: development cohort, N/A: not available, val: validation cohort.*

* AUC and CI was only available

4.1.6. Performance of scores to predict 30-day neurological outcome

Among the 24 included studies, 7 reported neurological outcome at 30 days. (96, 97, 120, 123, 132, 135, 140) Only three scoring systems - OHCA, rCAST, and SOFA - provided sufficient data for quantitative synthesis. The rCAST score yielded the highest pooled AUC (0.84; 95% CI, 0.68-0.99), whereas SOFA showed the lowest (0.67; 95% CI, 0.46-0.89). No statistically significant differences were observed between the pooled AUC estimates. Results are presented in Figure 9.

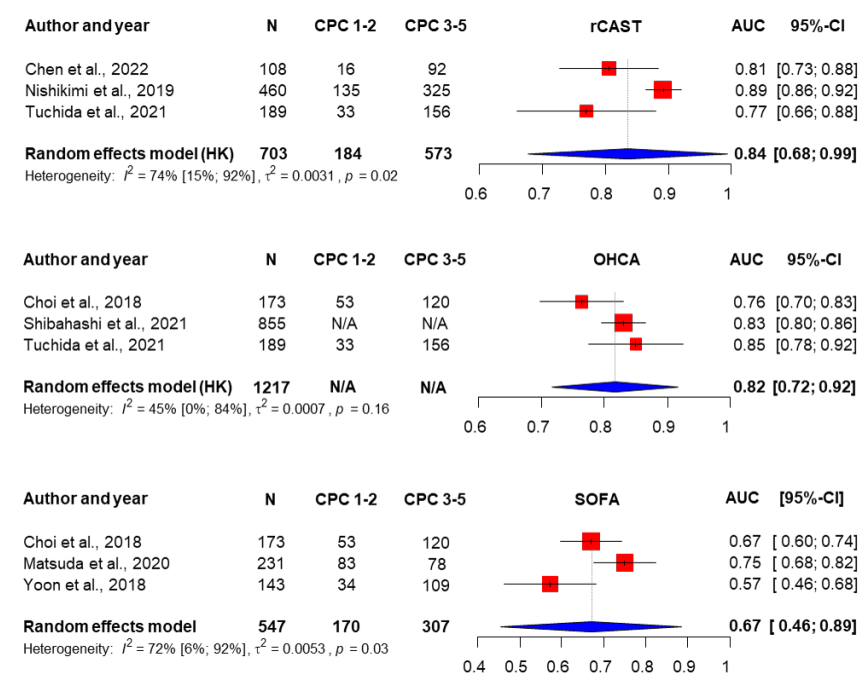


Figure 9. Random-effects pooled AUC of ROC curves and heterogeneity test for rCAST, OHCA and SOFA scores predicting 30-day neurological outcome.

AUC: area under curve, CI: confidence interval, CPC: cerebral performance category, N/A: not available.

4.1.7. Performance of scores to predict 6-months neurological outcome

Among the 24 included studies, 4 reported neurological outcome at 6 months. (102, 110, 119, 127) Only three scoring systems - CAHP, OHCA, and TTM - provided sufficient data for meta-analysis. The TTM score demonstrated the highest pooled AUC (0.880; 95% CI, 0.844-0.916), whereas the OHCA score had the lowest (0.811; 95% CI, 0.759-0.863). All analyses showed very high heterogeneity ($I^2 = 98-100\%$). Pairwise comparison indicated a significantly higher AUC for TTM than for OHCA ($p=0.0056$). Results are presented in Figure 10.

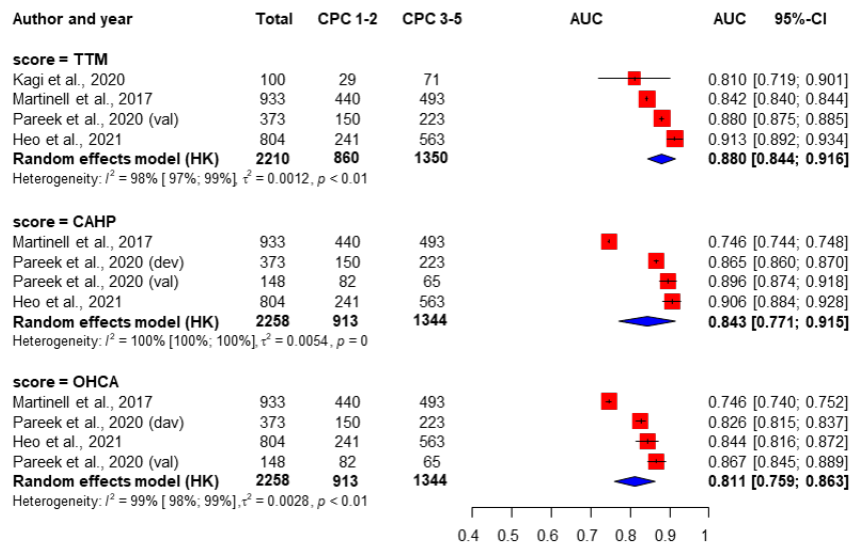


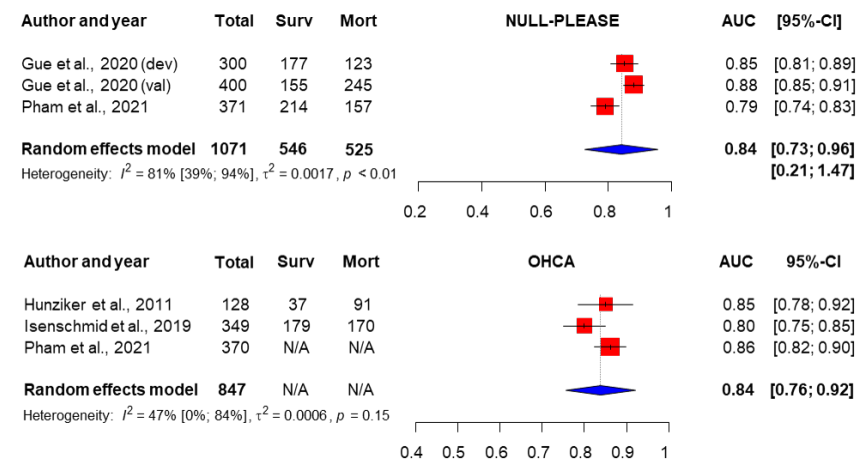
Figure 10. Random-effects pooled AUC of ROC curves and heterogeneity test for TTM, OHCA and CAHP scores predicting 6-month neurological outcome.

AUC: area under curve, CI: confidence interval, CPC: cerebral performance category, dev: development cohort, N/A: not available, val: validation cohort.

4.1.8. Additional analyses

We identified 4 studies that reported in-hospital mortality and 3 studies that investigated 30-day mortality as a clinical outcome (33, 36, 40, 42, 65). We found identical pooled AUC values for the OHCA score (0.84, 95% CI, 0.76-0.92) and NULL-PLEASE score (0.84, 95% CI, 0.73-0.96) to predict in-hospital mortality. In case of 30-day mortality the pooled AUC of SOFA score was 0.71 (95% CI 0.40-1.02) for the investigated endpoint. The results of the analyses are shown in Figure 11.

(A) In hospital mortality



(B) 30-day mortality

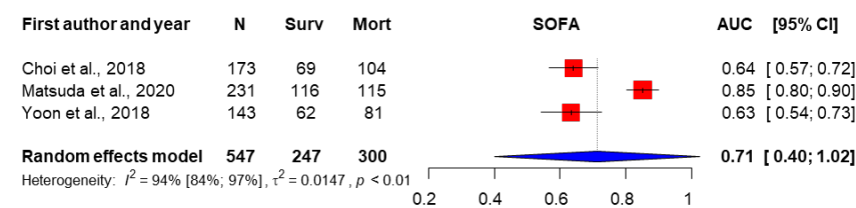


Figure 11. Random-effects pooled AUC of ROC curves and heterogeneity test for NULL-PLEASE and OHCA scores predicting in-hospital mortality and SOFA score predicting 30-day mortality. *AUC: area under curve; CI: confidence interval; CPC: Cerebral Performance Category; dev: development cohort; mort: mortality; N: number; N/A: not available; ROC: receiver-operating characteristic; surv: survival; val: validation cohort.*

Using the Steinhauser and Rücker approach, we generated SROC curves with confidence intervals for two scoring systems - CAHP and OHCA - for prediction of neurological outcome at hospital discharge. (85) This method could not be applied to the remaining scores because the included manuscripts did not provide sufficient sensitivity and specificity data across multiple thresholds. The corresponding results are presented in Figure 12.

We additionally evaluated CAHP and OHCA using randomly selected thresholds, repeating the analysis 16 times; these sensitivity analyses consistently demonstrated superior performance of CAHP compared with OHCA in the high-specificity range. For predefined thresholds (CAHP: 200 and 150; OHCA: 60 and 40), we calculated pooled sensitivity and specificity. At a CAHP threshold of 200, the pooled sensitivity was 0.45 (95% CI, 0.38-0.53) and the pooled specificity was 0.947 (95% CI, 0.924-0.964). Further details are shown in Figure 13.

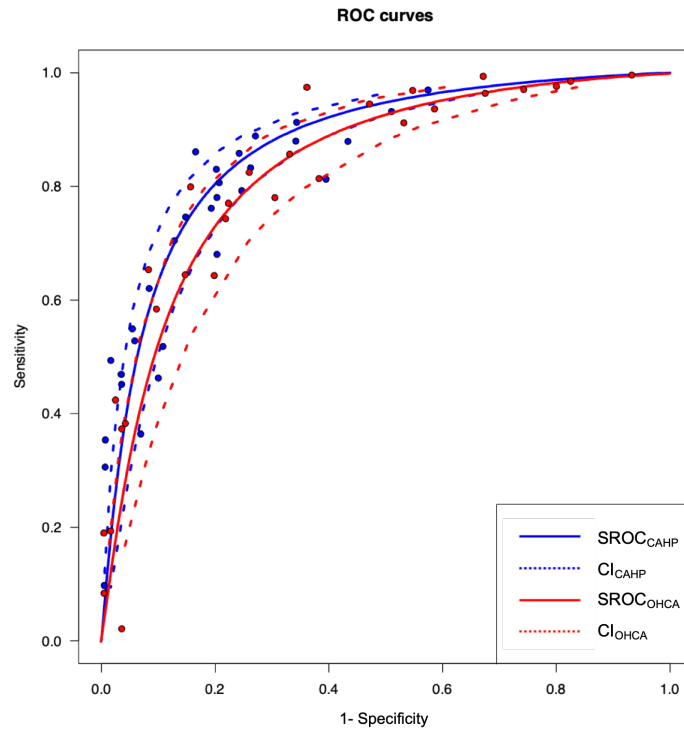


Figure 12. SROC curves along with confidence intervals using the method introduced by Steinhauser and Rücker. (85) *The continuous red curve is the SROC curve for the CAHP score system, and the dotted red curve is the corresponding CI. The continuous blue curve is the SROC curve for the OHCA score system, and the dotted blue curve is the corresponding CI. The blue and red dots marks the sensitivity and specificity values given by the individual studies included in the analysis at a fixed threshold.*

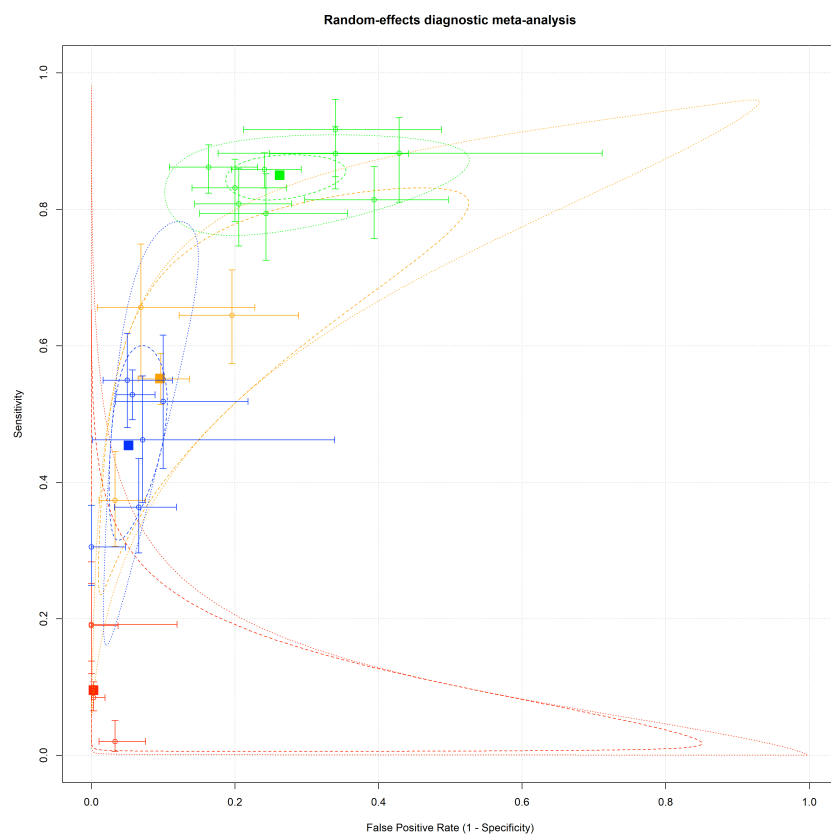


Figure 13. Visualisation of pooled sensitivity and sensitivity analysis of CAHP and OHCA scores at fix threshold. Different colours marks the fixed thresholds: green - CAHP “ ≥ 150 ”; blue - CAHP “ ≥ 200 ”, orange - OHCA “ ≥ 40 ”, red - OHCA “ ≥ 60 ”. The dotted line marks the prediction interval and the dashed line marks the confidence interval of the pooled sensitivity and specificity pair in each fix threshold.

4.2. Results of age–treatment interactions in OHCA

4.2.1. Study population and baseline characteristics

A total of 147,962 adult OHCA cases were analysed. Overall survival to hospital admission was 8.8% (n=12,975). Patient age ranged from 18 to 107 years (mean 69.6 ± 14.4), and 99,576 individuals (67.3%) were classified as elderly (≥65 years).

Baseline characteristics of the population presented in Table 5. stratified by age group. In the overall population, male sex was more common than female (58.7% vs. 41.3%, $p < 0.001$), cardiac arrest more frequently occurred at home, and initial rhythm more likely non-shockable. The prevalence of VF or VT was significantly lower in elderly patients (10.6% vs. 14.5 %, $p < 0.001$), while asystole was more common for the elderly (68.3 % vs. 70.8%, $p < 0.001$). The AED equipment availability were similar between groups. The median EMS response time was identical in both groups (11.8 min). The difference of distribution and mean values reached statistical significance because of the large sample size but it is clinically non relevant.

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Table 5. Baseline characteristics of study population

Characteristics	Overall (N = 147,962)	Non-elderly < 65 (N = 48,386)	Elderly ≥ 65 (N = 99,576)	p-value
Demographics				
Age, mean ± SD (years)	69.6 ± 14.4	53.4 ± 9.6	77.5 ± 8.4	<0.001
Male sex, n (%)	86,858 (58.7%)	34,850 (72.0%)	52,008 (52.2%)	<0.001
Survived to admission, n (%)	12,975 (8.8%)	5669 (11.7%)	7306 (7.3%)	<0.001
Initial Cardiac Rhythm				
VF/VT, n (%)	17,576 (11.9%)	7003 (14.5%)	10,573 (10.6%)	<0.001
PEA, n (%)	25,260 (17.1%)	7867 (16.3%)	17,393 (17.5%)	<0.001
Asystole, n (%)	103,590 (70.0%)	33,043 (68.3%)	70,547 (70.8%)	<0.001
Bradycardia, n (%)	1536 (1.0%)	473 (1.0%)	1063 (1.1%)	<0.001
AED Equipment and Usage				
AED equipment available, n (%)	118,067 (79.8%)	38,615 (79.8%)	79,452 (79.8%)	0.943
AED rhythm analysed, n (%)	3339 (2.3%)	1281 (2.6%)	2058 (2.1%)	<0.001
AED shock delivered, n (%)	972 (0.7%)	474 (1.0%)	498 (0.5%)	<0.001
EMS response time				
EMS response time, median ± IQR (min)	11.8 (7.5-18.2)	11.8 (7.5-17.6)	11.8 (7.5-18.5)	<0.001

4.2.2. Age-stratified survival outcomes

The primary analysis demonstrated a marked inverse association between age and survival, with clear implications for geriatric emergency care. As shown in Figure 14, age-stratified survival declined steadily with increasing age, following an approximately linear pattern from younger to older groups.

Using the 65-year cutoff, a pronounced survival gap was observed: survival was 7.3% among patients aged ≥ 65 years compared with 11.7% in those aged <65 years. This disadvantage was evident across initial rhythms and clinical presentations, supporting age as a key prognostic determinant beyond arrest characteristics.

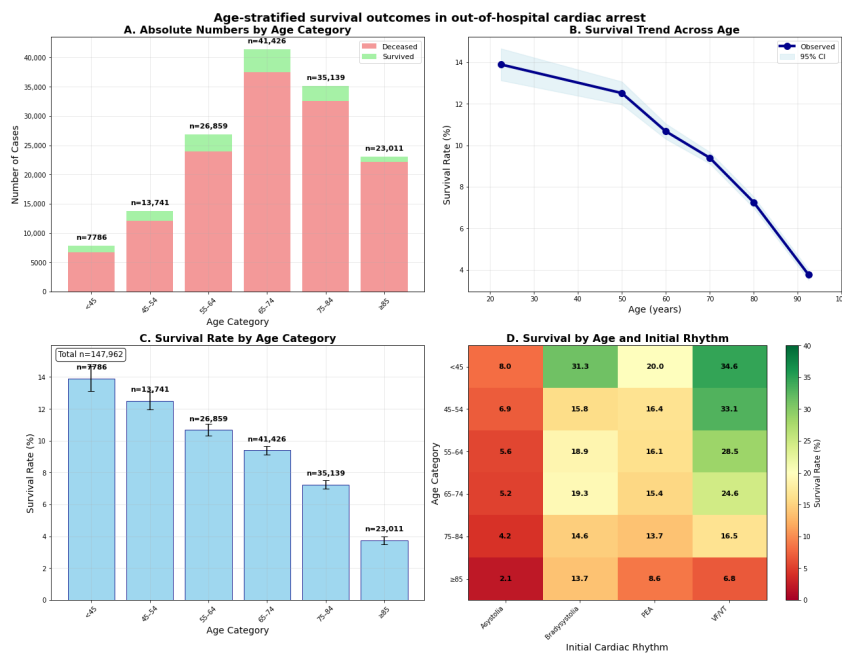


Figure 14. Age-stratified survival outcomes in out-of-hospital cardiac arrest. Comprehensive visualization of patient outcomes and survival patterns across age groups. Panel (A) summarizes absolute case counts and outcomes across age categories. Panel (B) depicts the continuous association between age and survival probability with 95% CI. Panel (C) presents age-group-specific survival rates with CIs. Panel (D) stratifies survival simultaneously by age group and initial rhythm.

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4.2.3. Individual predictors of survival: univariate analysis

Before multivariable adjustment, univariate analyses demonstrated significant associations between survival and several key clinical variables. Shockable rhythms were the most powerful predictors, with substantially higher survival compared with asystole (reference category). Arrests witnessed by medical personnel were also strongly associated with improved survival. The effects of advanced interventions were heterogeneous (Table 6.).

Delivery of an AED shock showed a particularly strong univariate association with survival, reflecting both the underlying arrest phenotype (i.e., shockable rhythm) and the therapeutic benefit of early defibrillation. Increasing age was associated with worse outcome, with each additional year reducing the odds of survival by approximately 2%, alongside further variability across presenting characteristics and EMS response factors.

Table 6. Univariate predictors of survival to hospital admission.

Variable	OR	95% CI	p-value	Clinical context
Age (per year)	0.98	0.979–0.981	<0.001	2% survival decrease per one year increase
Female sex (vs. male)	1.21	1.16–1.26	<0.001	Protective effect across ages
VF/VT (vs. asystole)	4.18	4.01–4.36	<0.001	Strongest individual predictor of survival
PEA (vs. asystole)	2.31	2.17–2.46	<0.001	Intermediate prognosis
Bradycardia (vs. asystole)	2.22	1.95–2.54	<0.001	Better than asystole
Medical personnel witness (vs. none)	2.74	2.63–2.85	<0.001	Professional early intervention
Non-medical bystander witness (vs. none)	1.55	1.47–1.63	<0.001	Early recognition and BLS
AED shock delivered (vs. no shock)	9.9	8.72–11.24	<0.001	Combined selection and treatment effect
Urban location (vs. rural)	1.33	1.26–1.40	<0.001	Healthcare access advantage
Public location (vs. home)	2.12	2.02–2.22	<0.001	Rapid recognition and EMS access
EMS response time (per min)	0.99	0.990–0.991	<0.001	Time-dependent decline in survival

4.2.4. Multivariate model: independent predictors of survival

After adjustment for confounding variables, the multivariate model included 13 clinically meaningful predictors and demonstrated good discriminatory performance (AUC = 0.784; 95% CI, 0.780–0.788) along with satisfactory calibration (Brier score = 0.0705). Adjusted odds ratios are illustrated in the Forest plot in Figure 15, with detailed effect estimates provided in Table 6.

The multivariable analysis identified VF/VT as the strongest independent predictor of survival (adjusted OR 5.34; 95% CI, 5.10-5.60). This was followed by arrests witnessed by medical personnel (OR 4.52; 95% CI, 4.29-4.77), bradycardia (OR 4.41; 95% CI, 3.82-5.08), and AED shock delivery (OR 3.52; 95% CI, 3.05-4.06). Age remained independently associated with outcome, with each additional year corresponding to an approximately 2% reduction in the odds of survival (OR 0.98; 95% CI, 0.98-0.98).

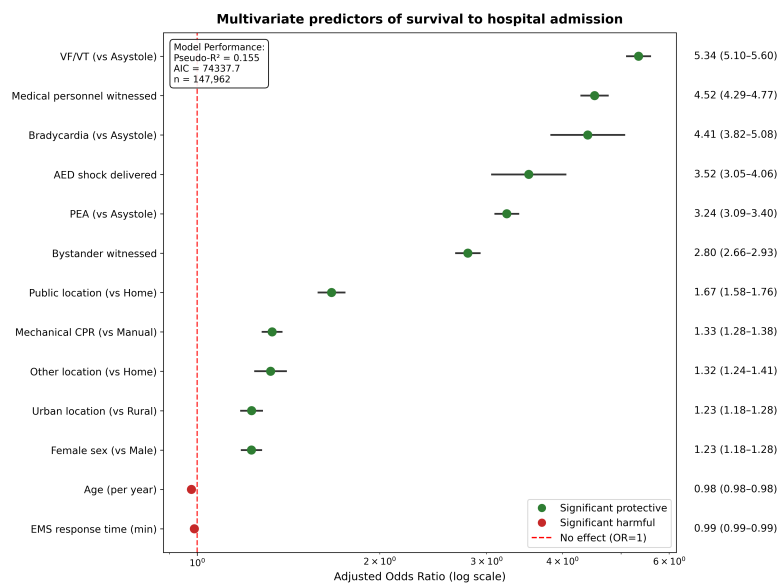


Figure 15. Multivariate predictors of survival to hospital admission. *Forest plot shows adjusted odds ratios and 95% confidence intervals for independent predictors of survival in the final multivariate logistic regression model. Variables are ordered by effect magnitude, with protective factors (OR > 1, green points) and risk factors (OR < 1, red points) clearly distinguished,*

Table 7. Multivariate model: independent predictors of survival to hospital admission.

Variable	Adjusted OR	95% CI	p-value	Clinical interpretation, effect on survival
Initial cardiac rhythm vs. asystole				
VF/VT (vs. asystole)	5.34	5.10–5.60	<0.001	Strongest predictor—shockable rhythm
Bradycardia (vs. asystole)	4.41	3.82–5.08	<0.001	Intermediate prognosis
PEA (vs. asystole)	3.24	3.09–3.40	<0.001	Better than asystole, worse than VF/VT
Witness and early intervention				
Medical personnel witness	4.52	4.29–4.77	<0.001	Professional early intervention
AED shock delivered	3.52	3.05–4.06	<0.001	Definitive defibrillation therapy
Non-medical bystander witness	2.8	2.66–2.93	<0.001	Early recognition and BLS
Location and demographics				
Urban location (vs. rural)	1.23	1.18–1.28	<0.001	Healthcare access advantage
Public location (vs. home)	1.67	1.58–1.76	<0.001	Rapid recognition and EMS access
Other location (vs. home)	1.32	1.24–1.41	<0.001	Non-home environment advantage
Female sex (vs. male)	1.23	1.18–1.28	<0.001	Persistent protective effect
Mechanical chest compression (vs. manual)	1.33	1.28–1.38	<0.001	Modest benefit for prolonged CPR
Time-dependent factors				
EMS response time (per min)	0.99	0.99–0.99	<0.001	Time-dependent mortality increase
Risk factors				
Age (per year)	0.98	0.98–0.98	<0.001	Progressive survival decline

4.2.5. Age interaction analysis: treatment effect modification

A key novel observation emerged from the prespecified evaluation of age-treatment interactions using robust statistical methods. After controlling for multiple comparisons with false discovery rate (FDR) correction, two interaction terms remained significant, indicating that the magnitude of several effects differs meaningfully across age strata (Figure 16). The most clinically relevant interaction was observed between female sex and age (interaction OR 0.882; 95% CI, 0.859-0.906; FDR-adjusted $p < 0.001$). In addition, the VF/VT and age interaction (OR 0.914; 95% CI, 0.887-0.943; FDR-adjusted

$p < 0.001$) showed that although shockable rhythm was associated with the highest survival across all ages, their relative survival advantage diminished in older patients.

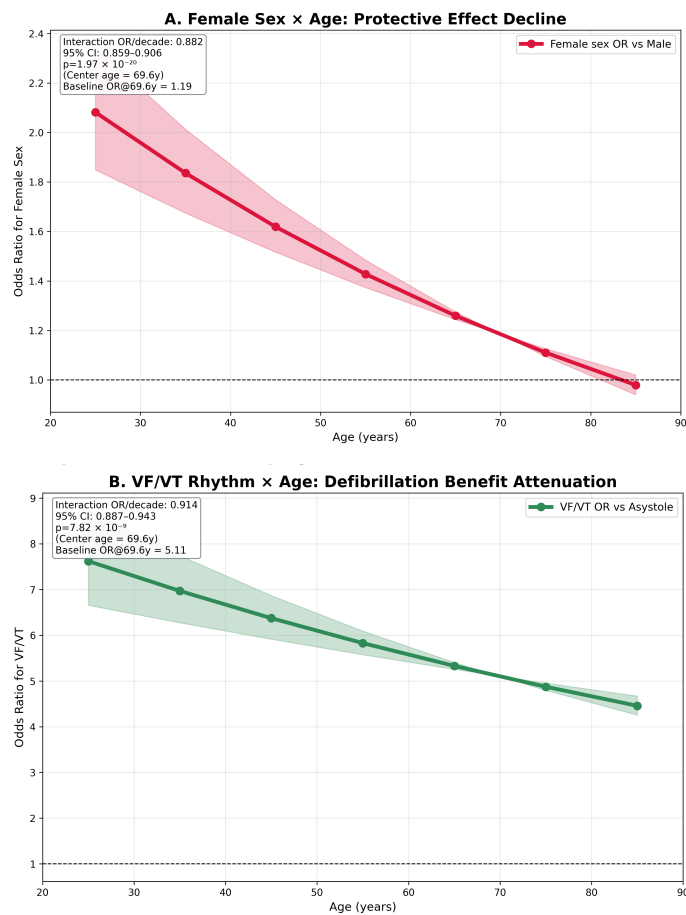


Figure 16. Age interaction analysis: treatment effect modification by age. A detailed visualization of the significant age–treatment interactions illustrates that the strength of key predictors changes across the age continuum. Panel (A) indicates that the survival advantage associated with female sex diminishes with increasing age. Panel (B) shows a similar age-related attenuation in the survival benefit of VF/VT, although a shockable rhythm remains the most influential independent predictor across all ages. Estimates are based on multivariable logistic regression with continuous age interaction terms, centred at the cohort mean age (69.6 years) and scaled per 10-year increase.

4.2.6. Clinical impact and model performance

The final model showed strong predictive performance and retained clinical usefulness across a range of decision thresholds. As summarized in Table 8, overall discrimination and calibration were good. Model stability was supported by five-fold cross-validation, suggesting good generalizability with minimal evidence of overfitting.

Assessment of potential clinical impact using number needed to treat (NNT) highlighted meaningful effects of key interventions. AED shock delivery yielded the greatest benefit (NNT = 3), followed by arrest witnessed by medical personnel (NNT = 10); a non-medical bystander witness also conferred a clinically relevant advantage (NNT = 26).

Age-stratified analyses further indicated that, although absolute survival declined with advancing age, the relative benefit of the principal interventions remained appreciable across age groups.

Table 8. Model performance and population impact metrics.

Performance metric	Value	95% CI	Clinical interpretation
Discrimination			
AUC	0.784	0.780–0.788	Overall discrimination
Cross-validation AUC	0.784	0.781–0.787	5-fold stratified CV
Calibration			
Brier Score	0.0705	0.0702–0.0709	Overall calibration (lower is better)
Hosmer–Lemeshow <i>p</i> -value	0.082		Goodness-of-fit (higher suggests no lack of fit)
Clinical utility (at optimal threshold)			
Sensitivity	73.9%	73.2–74.6%	Case detection
Specificity	68.6%	68.4–68.9%	Rule-out performance
PPV	18.4%	18.2–18.7%	Positive predictive value
NPV	96.5%	96.4–96.6%	Negative predictive value

Table 8. Model performance and population impact metrics (cont.).

Population impact (ARD & PIF)			
AED shock delivered - ARD (pp)	13.09	10.99–15.43	Adjusted absolute survival gain (percentage points) if universally applied vs. none
AED shock delivered - PIF (universal, %)	147.5	124.1–174.0	Projected relative increase in overall survival with universal exposure
Medical personnel witness - ARD (pp)	11.23	10.75–11.73	Adjusted absolute survival gain (percentage points) if universally applied vs. none
Medical personnel witness - PIF (universal, %)	78.6	74.3–83.2	Projected relative increase in overall survival with universal exposure
Non-medical bystander witness - ARD (pp)	6.33	6.04–6.63	Adjusted absolute survival gain (percentage points) if universally applied vs. none
Non-medical bystander witness - PIF (universal, %)	22.6	20.6–24.9	Projected relative increase in overall survival with universal exposure

5. Discussion

5.1. Prediction performance of scoring systems after OHCA

Our objective was to review all the prognostic scoring systems designed to estimate outcome in successfully resuscitated adult OHCA patients during the early post-admission period, using variables that are readily available from basic tests, medical history, and resuscitation data. Although numerous tools have been published, both the scoring systems themselves and the underlying patient cohorts proved highly heterogeneous, limiting direct comparability.

The literature search identified two systematic reviews and one prior meta-analysis addressing prognostic scores in OHCA and/or IHCA populations. One review concluded that formal meta-analysis was not feasible because of substantial between-score differences. Amacher and colleagues pooled C-statistics for only three scores (OHCA, CAHP, and GO-FAR) and reported acceptable prognostic accuracy for OHCA and CAHP, but without stratification by endpoint timing. (141, 142, 143)

In our systematic review, we summarized all the available prognostic scores for adult OHCA survivors, with particular emphasis on predictors that can be obtained immediately at ICU admission. However, predictor selection varied widely: the number of variables per score ranged from very few to complex multi-parameter models. Importantly, over 60% of included studies were based on cohorts assembled before publication of the TTM trial, which substantially reshaped post-cardiac arrest management and may therefore affect both baseline prognosis and model performance. (144)

A key finding was a statistically significant difference among scores predicting neurological outcome at hospital discharge. For CAHP, C-GRaPH, and OHCA, pooled AUC analyses - and complementary SROC evaluation where feasible - supported meaningful discrimination. By conventional AUC categories, CAHP and OHCA demonstrated “good” performance, but CAHP showed clear superiority over OHCA, particularly in the high-specificity region. This is clinically important because early prognostic tools should primarily avoid false-positive classification of poor outcome, which could contribute to premature withdrawal of life-sustaining treatment.

For 30-day neurological outcome, available data supported meta-analysis for OHCA, rCAST, and SOFA; rCAST and OHCA performed in the “good” range, whereas SOFA was lower and supported by smaller datasets. For 6-month neurological outcome, pooled

results suggested “good” discrimination for TTM, CAHP, and OHCA, though very high heterogeneity and limited study numbers precluded more advanced comparative analyses. Based on pooled AUC values, CAHP emerged as the most useful one overall, followed by C-GRaPH and then OHCA. CAHP and C-GRaPH scored favorably in terms of predictor availability because most inputs are accessible prehospital or immediately after arrival. In contrast, OHCA requires a laboratory parameter, delaying complete score calculation. From an operational perspective, C-GRaPH is simple to compute using dichotomous predictors, CAHP uses a point-based scale, while OHCA relies on a logarithmic formula, which may further reduce bedside practicality.

Strengths of this work include prospective protocol registration, adherence to predefined methods, and the use of multiple analytical approaches to improve robustness. To our knowledge, this is among the first studies to quantitatively compare and rank these widely used prognostic tools. Key limitations are the predominance of retrospective cohorts, limited availability of threshold-specific diagnostic accuracy data, and substantial heterogeneity in both score design and outcome definitions, which restricted the number of tools eligible for meta-analysis. Additionally, prediction models may not transport well across settings; calibration and discrimination can vary by population, EMS systems, and post-resuscitation care pathways, underscoring the need for broader external validation.

For clinical practice, prognostic scores may provide objective, reproducible information to support clinician judgment and communication with relatives, but they should not be used in isolation. Early admission variables cannot be used as the only tool for prognostication, and it would be unethical to base WLST solely on a score. Guideline-consistent prognostication requires a multimodal approach, typically after clearance of confounders such as sedation and temperature control. Future research should prioritize prospective validation of scoring systems in consecutive real-world cohorts, include sensitivity/specificity analyses at clinically relevant high-specificity thresholds, and evaluate whether integrating biomarkers improves the performance. Several included studies already suggest potential benefit from such biomarker addition to scores. (105, 118, 134) Finally, the evidence base remains sparse in several world regions (notably parts of Africa and South America), indicating an important global gap in OHCA surveillance, post-cardiac arrest care data, and prognostic research.

5.2. Age-treatment interactions in OHCA

This nationwide, registry-based analysis provides a large-scale and granular assessment of age-specific outcomes, independent predictors, and age-related effect modification in OHCA. Using 147,962 adult cases with attempted resuscitation, we observed a strong and progressive inverse association between age and survival: each additional year of age was associated with an approximately 2% reduction in the odds of survival. The decline was evident across the full age spectrum and is consistent with the multifactorial vulnerability of older patients, including higher comorbidity burden, reduced physiological reserve, and less favorable arrest phenotypes. Importantly, our results indicate that age is not only a prognostic factor in itself, but also modifies the magnitude of benefit associated with several key predictors and interventions.

A central clinical observation was the markedly lower prevalence of shockable rhythms among elderly patients and the predominance of asystole. Because VF/VT was the strongest independent predictor of survival in adjusted analyses, its reduced occurrence in older patients inherently limits the proportion who can benefit from defibrillation. Strategies that shorten time to recognition of cardiac arrest, dispatch activation, and first shock may be particularly important in elderly populations, where delays, comorbidities, and atypical presentations may allow initially shockable rhythms to deteriorate into non-shockable rhythms or may increase the likelihood of primary PEA/asystole. These findings support the preventive approaches and earlier detection in high-risk elderly groups, including the potential role of remote monitoring and proactive follow-up in patients with known cardiovascular disease.

Female sex was associated with better survival overall, but the protective effect declined with advancing age, implying that sex-related differences should be interpreted within an age-specific framework rather than assumed to be constant throughout the lifespan. Similarly, the survival advantage associated with VF/VT remained substantial across all ages but was attenuated in older patients, highlighting clinically meaningful effect modification even for the strongest survival predictors.

Despite these age-related attenuations, several time-critical interventions showed high benefit across the entire age continuum. AED shock delivery showed the most favorable clinical impact, with a very low number needed to treat (NNT = 3) and minimal difference between elderly and non-elderly patients (3.2 vs 2.8). This supports the principle that

public-access defibrillation should be maintained and promoted without age-based restrictions, and that AED deployment strategies should explicitly include settings relevant to older adults. Witness presence also remained highly consequential: arrests witnessed by medical personnel conveyed a major survival benefit (NNT = 10), and even OHCA witnessed by non-medical bystander was associated with clinically meaningful improvement (NNT = 26). Together, these results reinforce that strengthening the early links of the chain of survival benefits patients of all ages, including the elderly, and that the largest survival benefit is based rapid recognition, prompt initiation of CPR, and early defibrillation when indicated.

Methodologically, the identification of significant age–treatment interactions provides an empirical basis for developing geriatric-tailored resuscitation strategies while simultaneously confirming that basic interventions remain effective across age groups. In addition, the predictive performance of our multivariable model supports its potential use as a component of real-time decision support, enabling age-adjusted prognostication at the point of care.

From an ethical and health-system perspective, these findings align with the ERC statement that chronological age alone should not guide resuscitation intensity, because older patients continue to derive meaningful benefit from evidence-based interventions, especially defibrillation. Nevertheless, real-world care may diverge from this principle: prior case–control data suggest that older OHCA patients may receive shorter and less intensive prehospital care, raising concern that age-related treatment attenuation could contribute to worse outcomes. This underscores the importance of protocol-driven practice, transparent decision-making, and quality assurance systems designed to prevent underpowering ICU therapy based on elderly age. (44)

Implementation should also reflect where many elderly arrests occur: predominantly at home and within municipal veteran or home-care contexts. Qualitative evidence indicates that limited organizational support, constrained care alternatives, and insufficiently structured collaboration between municipal care personnel and EMS may impair emergency response; conversely, well-prepared caregiving staff can act as effective patient representatives and facilitate EMS engagement. (145)

Practically, this supports strengthening early response capacity for older adults through: (i) targeted AED placement and improved AED access in high-risk elderly communities;

(ii) tailored training, clear role delineation, and structured handover processes for home-care and municipal staff to accelerate recognition, calling, CPR/AED initiation, and EMS transition; and (iii) audit and feedback mechanisms that monitor equitable delivery of time-sensitive interventions across age strata.

Several limitations follow from the retrospective, registry-based design. First, the primary endpoint was survival to hospital admission; while this reduces confounding from in-hospital variability, it does not capture longer-term survival or neurological outcomes. Second, the multivariable model was constrained to variables reliably recorded in the EMS registry; comorbidities and pre-arrest functional status were not systematically available. Bystander CPR was not included in the model due to data loss and potential statistical bias, witness status served as the available proxy of early recognition. Third, we excluded certain intra-arrest interventions (e.g., drug administration) from the primary prediction model to avoid resuscitation time bias, as these measures may reflect prolonged resuscitation attempts rather than independent predictors early in the course. Finally, system-level disruptions (including pandemic-related effects) may have influenced case mix and outcomes.

Future research should link EMS data to in-hospital care and long-term follow-up to evaluate neurologically intact survival, functional status, and the relative contribution of prehospital versus in-hospital factors to age-related disparities. Incorporating frailty and functional measures into registries may improve age-specific risk estimation and reduce unmeasured confounding. Before clinical implementation, the prediction model requires external validation and recalibration in independent EMS systems, given that model performance and calibration can vary materially across populations and care pathways.

6. Conclusion

Based on our findings, CAHP provides the most accurate prediction of neurological outcome at hospital discharge and is slightly less accurate than the TTM score for 6-month outcomes. We support the use of CAHP in routine clinical practice, not only because of its strong overall accuracy and superior specificity, but also because the variables required for calculation are rapidly and readily obtainable at or shortly after admission. The OHCA score also demonstrated consistently good performance for predicting neurological outcome both at hospital discharge and at 6 months after arrest. Looking ahead, prospective, consecutive registry-based data collection using standardized and reproducible methods is needed to enable robust comparison and external validation of prognostic scores in cardiac arrest populations.

In the nationwide HNAS registry of 147,962 adult OHCA cases, increasing age was independently associated with a progressive reduction in survival to hospital admission. Nevertheless, time-critical interventions - most notably early defibrillation - remained strongly beneficial across the age spectrum, supporting resuscitation decisions guided by clinical characteristics rather than chronological age alone. The observed age-related effect modification further underscores the need for geriatric-adapted systems of care that prioritize rapid recognition and timely shock delivery. Given the model's performance, development of a real-time, age-adjusted risk stratification tool appears feasible, but should be pursued only after external validation and appropriate recalibration.

7. Summary

This thesis summarizes outcome prediction and age-related determinants in OHCA through two linked research components: a systematic review and meta-analysis of prognostic scoring systems and a nationwide HNAS registry analysis focused on age–treatment effect modification.

The systematic review identified 51 eligible studies (86,321 patients) describing 36 prognostic scoring systems or models; 24 studies (13,261 patients) were included in quantitative synthesis. Predictor sets and cohorts were highly heterogeneous, and most datasets predated major shifts in post-resuscitation care (e.g., widespread targeted temperature management). Across scores eligible for meta-analysis, neurological outcome at hospital discharge was most frequently reported. CAHP demonstrated the highest pooled discrimination for poor neurological outcome at discharge (AUC 0.876; 95% CI, 0.853–0.898), while C-GRaPH showed the lowest (AUC 0.764; 95% CI, 0.738–0.791). Additional SROC and threshold-based analyses supported CAHP’s superior performance in high-specificity ranges, consistent with a “rule-in poor outcome” use case.

The registry analysis included 147,962 adult OHCA patients with attempted resuscitation (2018–2025), with 8.8% survival to hospital admission. Increasing age was associated with a progressive survival disadvantage (2% lower odds per year). VF/VT, medical witness, bradycardia, and AED shock delivery were the strongest independent predictors; the final multivariable model showed good discrimination (AUC 0.784) and calibration. After false discovery rate correction, significant age interactions indicated attenuation of the survival advantage associated with female sex and shockable rhythm with advancing age, while time-critical interventions retained substantial benefit across age strata.

The thesis concludes that CAHP is the most robust early score for discharge neurological outcome prediction and that age influences both baseline prognosis and the magnitude of certain predictors, yet should not drive therapeutic neglect. It emphasizes standardized registry-based validation, high-specificity performance reporting, and external validation/recalibration before implementation of real-time decision-support tools.

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