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Prognostic Value of Arterial Blood Gas Analysis for Predicting Survival and Neurological Outcomes in Cardiac Arrest Patients

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Zusammenfassung

Der Herzstillstand weist hohe Mortalitätsraten und meist schlechte neurologische Folgen bei den Überlebenden auf. Die Prognose anhand klinischer Merkmale ist schwierig und erfolgt häufig mithilfe komplexer Scoresysteme. Das primäre Ziel dieser Arbeit war es, die prognostische Aussagekraft der während der kardiopulmonalen Reanimation erhobenen arteriellen Blutgasparameter, einzeln oder in Kombination, hinsichtlich der Krankenhaus- und 30-Tage-Mortalität zu untersuchen. Das sekundäre Ziel war es, den prädiktiven Wert arterieller Blutgasparameter für die neurologischen Folgen bei Krankenhausüberlebenden zu bewerten.

742 Patienten mit nichttraumatischem Herzstillstand, die zwischen 2013 und 2017 im Universitätsklinikum Düsseldorf stationär aufgenommen wurden, wurden retrospektiv analysiert. Der prädiktive Wert jedes arteriellen Blutgasparameters für die Krankenhausmortalität wurde mittels Receiver-Operating-Charakteristik (ROC) Kurven analysiert. Variablen mit guter prognostischer Genauigkeit wurden anschließend in Cox-Regressionsanalysen unter Berücksichtigung relevanter Kovariaten untersucht.

Laktat zeigte die höchste prognostische Genauigkeit (AUROC 0,83, p<0,0001), gefolgt von pH (AUROC 0,75, p<0,0001), Bikarbonat (AUROC 0,73, p<0,0001), Basenüberschuss (AUROC 0,74, p<0,0001) und Kalium (AUROC 0,69, p<0,0001). Die Youden-Indizes für Laktat- und pH-Werte betrugen 5,95 mmol/L bzw. 7,2007 (gerundet auf 7,20 und in den nachfolgenden Analysen verwendet). Subgruppenanalysen der Patientencharakteristika (Alter, Geschlecht), der Art des Herzstillstands sowie verschiedener Laktatwerte (als Indikator für *Hypoperfusion*) und Kohlendioxidpartialdrücke (als Indikator für *Ventilation*) zeigten ein erhöhtes Mortalitätsrisiko für Patienten mit schwerer Azidose (pH $\leq$7,2, HR 1,5–3). Korrelationsanalysen ergaben eine geringe bis moderate Kollinearität zwischen pH und Laktat (R^2=0,38, p<0,0001). Die Kombination aus pH-Wert und Laktatspiegel ermöglichte eine differenziertere Risikostratifizierung hinsichtlich der Krankenhaus- und der 30-Tage-Sterblichkeit (p<0,0001). In Cox-Modellen blieb der pH-Wert (sowohl kontinuierlich als auch dichotomisiert bei 7,20), unter Berücksichtigung von Laktat, Art des Herzstillstands, Alter und Geschlecht, signifikant mit der Mortalität assoziiert. Bei den Überlebenden des Krankenhausaufenthalts zeigte keiner der initial erhobenen arteriellen Blutgasparameter eine klinisch relevante Assoziation mit dem neurologischen *Outcome*.

Die initiale Blutgasanalyse von Patienten mit Herzstillstand kann helfen, die Krankenhaussterblichkeit vorherzusagen, insbesondere anhand des pH-Werts und des Laktatspiegels. Eine Azidämie sagt die intrahospitale Mortalität unabhängig von ihrer Ätiologie voraus, während die Kombination aus pH-Wert und Laktatspiegel eine präzisere Risikostratifizierung ermöglicht. Diese Ergebnisse unterstreichen das Potenzial der Blutgasanalyse zur Mortalitätsprädiktion, auch für den Einsatz im prähospitalen Setting.

Summary

Cardiac arrest is associated with high mortality rates and often severe neurological sequelae in survivors. Prognosis based on clinical characteristics is challenging and frequently relies on complex scoring systems. The primary objective of the current thesis was to investigate the prognostic value of arterial blood gas parameters, individually or in combination, obtained during cardiopulmonary resuscitation on in-hospital and 30-day mortality. The secondary objective was to assess the predictive value of arterial blood gas parameters on neurological outcome of hospital survivors.

742 patients with non-traumatic cardiac arrest admitted to Düsseldorf University Hospital between 2013 and 2017 were retrospectively analyzed. The predictive value of each arterial blood gas parameter for in-hospital mortality was analyzed using receiver operating characteristic (ROC) curves. Variables with good prognostic accuracy were subsequently examined using Cox regression analyses, taking relevant covariates into account.

Lactate showed the highest predictive accuracy (AUROC 0.83, p<0.0001), followed by pH (AUROC 0.75, *p*<0.0001), bicarbonate (AUROC 0.73, *p*<0.0001), base excess (AUROC 0.74, *p*<0.0001), and potassium (AUROC 0.69, *p*<0.0001). The Youden indices for lactate and pH were 5.95 mmol/L and 7.2007 mmol/L, respectively (rounded to 7.20 mmol/L and used in subsequent analyses). Subgroup analyses of patient characteristics (age, sex), type of cardiac arrest, and various lactate levels (as an indicator of hypoperfusion) and carbon dioxide partial pressures (as an indicator of ventilation) showed an increased mortality risk for patients with severe acidosis (pH ≤7.2, HR 1.5–3). Correlation analyses revealed low to moderate collinearity between pH and lactate (R^2 = 0.38, *p*<0.0001). The combination of pH and lactate levels allowed for more differentiated risk stratification with respect to in-hospital and 30-day mortality (*p*<0.0001). In Cox models, pH (both continuous and dichotomized at 7.20), remained significantly associated with mortality after adjusting for lactate, type of cardiac arrest, age, and sex. Among the survivors of hospitalization, none of the initially measured arterial blood gas parameters showed a clinically relevant association with neurological outcome.

Initial blood gas analysis in patients with cardiac arrest can aid to predict in-hospital mortality, particularly based on pH and lactate levels. Acidemia predicts in-hospital mortality regardless of its etiology, while the combination of pH and lactate levels allows for more precise risk stratification. These findings underscore the potential of blood gas analysis for mortality prediction, including in the prehospital setting.

Abbreviations

AED	Automatic external defibrillator
AIC	Akaike´s Information Criterion
ALS	Advanced life support
ASY	Asystole
AUC	Area under the curve
CPR	Cardiopulmonary resuscitation
ECG	Electrocardiogram
EEG	Electroencephalography
IHCA	In-hospital cardiac arrest
LFT	Low Flow Time
MAP	Mean arterial pressure
miRNA	MicroRNA
cNFT	No Flow Time
OHCA	Out-of-hospital cardiac arrest
PCT	Procalcitonin
PEA	Pulseless electrical activity
RCT	Randomized controlled trial
ROC	Receiver-operator curve
ROSC	Return of spontaneous circulation
SD	Standard Deviation
USA	United States of America
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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1 Introduction

1.1 Epidemiology and pathophysiology of the cardiac arrest

Cardiac arrest is defined as a life-threatening condition where the heart suddenly stops beating effectively, leading to an acute change in the hemodynamic cycle and a cessation of blood flow to the organs [1]. The condition occurs frequently across all societies and continents. Approximations show a rate as high as 15-20% of all deaths occurring in the United States of America (USA) and Western Europe to be attributed to cardiac arrest [2]. In Europe, it is considered the third leading cause of death [3, 4]. The multicentre prospective EuReCa one study, which focused on out-of-hospital cardiac arrest (OHCA), patients' characteristics, and the rapid initiation of cardiopulmonary resuscitation across 27 European countries, aiming to improve survival, showed an annual incidence of cardiac arrest in Europe of approximately 84 out of 100.000 individuals [3].

The high mortality following a cardiac arrest is explained by its pathophysiology. During cardiac arrest, the abrupt cessation of systemic circulation results in a global ischemic state, depriving all tissues of oxygen [5]. This initiates a cascade of cellular and metabolic derangements that are both time-dependent and organ-specific. Among all tissues, the brain is the most vulnerable to oxygen deprivation due to its high metabolic demands and limited energy reserves [6]. Neuronal injury begins within minutes of anoxia, leading to irreversible cell death due to depletion of high-energy substrates (adenosine triphosphate), ion exchange pumps, and mitochondrial dysfunction [7]. Upon initiation of cardiopulmonary resuscitation, which mimics the function of the heart, the circulation and conversely the cerebral blood flow is partially restored, but it remains suboptimal and contributes further to blood-brain barrier disruption and cerebral oedema. With the return of spontaneous circulation (ROSC), the cerebral blood flow is restored; however, reperfusion triggers a series of immune reactions and the generation of reactive oxygen species, leading to secondary brain injury [8]. Clinically, this is reflected in the high incidence of post-anoxic encephalopathy, which is the leading cause of mortality and morbidity in patients who achieve ROSC after cardiac arrest [9]. Cognitive impairment, coma, or persistent vegetative state are common sequelae, and the degree of neurological recovery remains the most critical determinant of long-term outcome [10]. Concomitantly, systemic hypoperfusion and global tissue hypoxia also result in ischemic injury to other vital organs, particularly the kidneys, liver, and myocardium. This can culminate in post-cardiac arrest syndrome, which is often characterized by a combination of severe brain injury, myocardial dysfunction, and multi-organ failure [11]. From a therapeutic and prognostical standpoint, time is the most

critical factor in limiting ischemic injury. Numerous studies have demonstrated a strong correlation between the duration of circulatory arrest, no-flow time, and consecutive time to initiation of cardiopulmonary resuscitation (CPR), as well as with both short- and long-term outcomes, including survival, neurological recovery, and quality of life. Efforts to restart systemic hemodynamics were one of the significant research and guideline implementation subjects of the last decades, and it is currently known as providing life support by CPR.

Depending on the place of manifestation, two forms of cardiac arrest are distinguished. OHCA occur outside of the hospital setting, such as at home or in public places. They display lower survival rates because life-saving measures are often delayed. Although resuscitation is attempted in 40-50% of cases with an average rate of bystander CPR of almost 58% [4], these measures are frequently not quickly enough initiated and not optimally carried out. Public access to automated external defibrillators can significantly improve survival rates, yet their accessibility remains relatively limited in many communities. As a consequence, survival after OHCA remains low. A meta-analysis of over 140 studies showed that only 8.8%[12] of OHCA patients survived to discharge. At the same time, a ROSC occurred in under one-third of patients, and survival to hospital admission was 22% [12]. Among survivors, about half experience limitations in everyday life as a consequence of hypoxic-ischaemic brain injury [4, 13]. Patients who successfully resuscitate from OHCA and are discharged from the hospital have a mean survival time of 5.4 years following this event, according to a systematic review and meta-analysis [14].

In-hospital cardiac arrests (IHCA) are defined as arrests occurring during the hospitalization of patients. It benefits from faster intervention and better infrastructure by medical professionals. At the same time, IHCA is often in direct link to a known severe underlying condition. Despite faster intervention, mortality is also high in this cardiac arrest form, and it is relevant in hospitalized patients. IHCA incidence ranges from 1 to 10 cases per 1000 hospital admissions [15]. Compared to OHCA, survival rates at 30 days range from 15 to 34% [4] in IHCA. Contemporary studies show higher survival in IHCA than in OHCA, but the neurological outcomes are similarly poor [16, 17].

1.2 Cardiopulmonary resuscitation

Providing life support by CPR is the clinical attempt to sustain a systemic circulation during the loss of the own giving time for identifying and reversing the initial underlying cause for cardiac arrest occurrence. The most important role of CPR is to reduce ischemic time, despite the high heterogeneity of characteristics encountered in CA. These variables have been extensively researched in both simulated and real-life models, yielding numerous recommendations. Considering all the specific measures of life support may appear

overwhelming to individuals without a medical background, the most important steps have been outlined in a straightforward algorithm, defined as basic life support. Importantly, since most CPRs are high-stress situations for healthcare providers and laypersons, algorithms for basic and the later-presented advanced life support (ALS) are presented in alphabetical order by the first five letters. These are displayed in Figure 1.

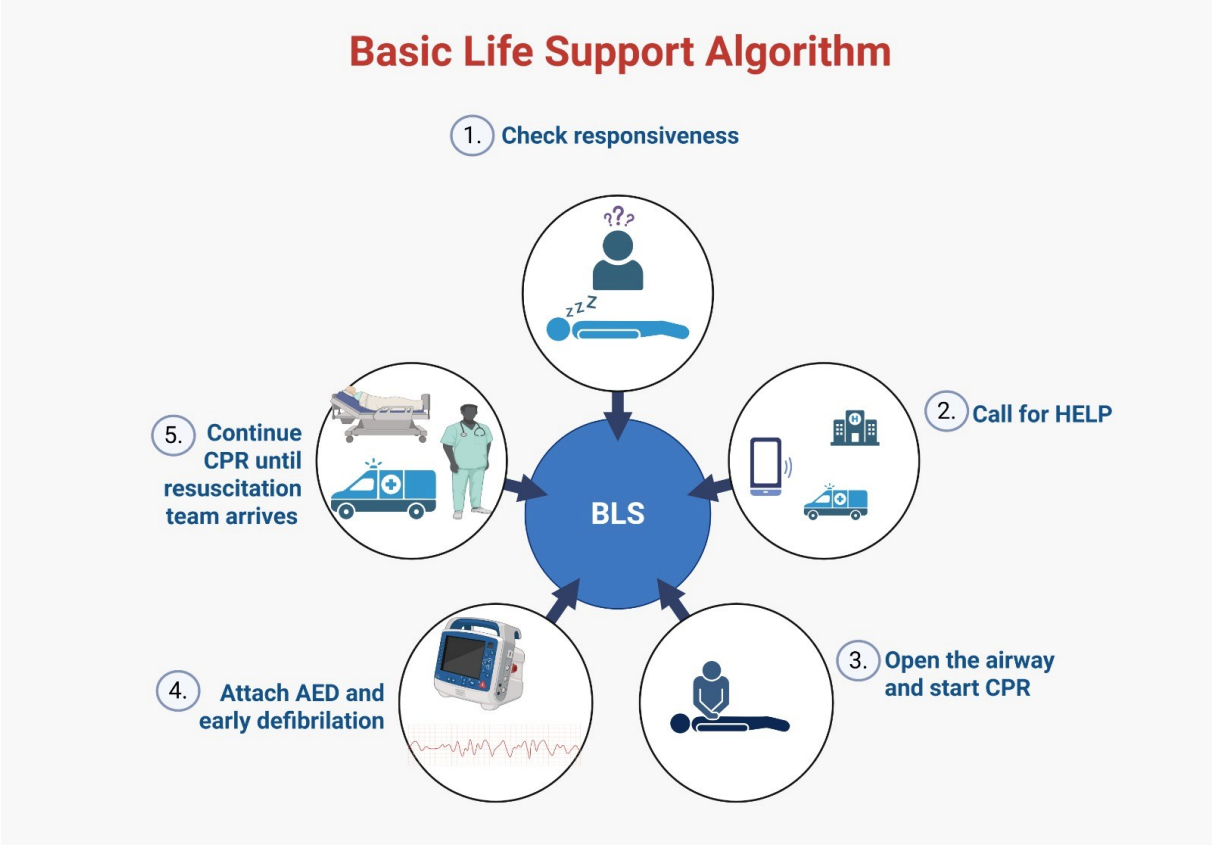

Fig. 1: Guideline recommendations for initial management of OHCA and IHCA. AED = automated external defibrillator; BLS = basic life support; CPR = cardiopulmonary resuscitation. Adapted after [18]. This figure was created in BioRender.

Briefly, basic life support is defined as early recognition of a cardiac arrest victim, performing 30 chest compressions at a depth of 5-6 cm and a frequency of about 100/minute, and, if available, the use of an automatic external defibrillator (AED). When performed correctly, almost everyone can provide basic life support, which helps reduce ischemic time by mimicking heartbeats and breathing attempts. Although chest compressions are an important technique to increase the survival rate in out-of-hospital cardiac arrest, outcomes improve significantly when the public has access to defibrillators. According to a British study, early defibrillation can increase the survival rate by up to 50-70% when it occurs within the first 3-5 minutes of collapse[19]. Therefore, the European Parliament addressed this problem in 2012 and recommended extensive programs for training laypeople and implementing AEDs in public spaces [4]. The BLS algorithm differs

between adults and children due to the cause of cardiac arrest. In adults, the cause is cardiac, while in children, it is commonly due to respiratory failure[20]. This difference is emphasized in the pediatric BLS sequence, which starts with 5 breaths followed by 15 compressions with 2 breaths, with a depth of 4 cm and a rate of 120/minute. A recent study performed in Rotterdam found as the most frequent cause of death in children drowning (28 %), followed by sudden infant death syndrome with 15% [21].

ALS was developed in 1970 by the American Heart Association and implies more specific recommendations to improve outcomes [22]. This includes early recognition of specific causes of CA, reversing them, and ensuring adequate circulation and oxygenation throughout the process. ALS was developed strictly for physicians and specialized healthcare providers because ensuring adequate oxygenation and ventilation, and identifying and promptly treating circulatory failure, often require invasive measures such as intubation or mechanical circulatory support. Non-invasive measures carried out by specialized personnel include the correct administration of fluids and medication. During ALS, providers need clear communication and dynamic teamwork. Often, high-quality ALS management is achieved when one of the physicians, usually the one with the most intensive care experience, assumes the role of team leader, maintains an overview of the entire situation, and clearly directs the remaining personnel on imminent tasks. Due to the complexity of the situation, which can occur at any time and in any place, most discipline societies have standardized training, intending to certify providers and enable them to act with high precision. Studies have shown that periodic training and certification improve the management of cardiac arrest and outcomes [23, 24].

ALS guidelines emphasize recognition and management of reversible causes for cardiac arrest. These include early recognition and treatment of hypoxia and hypercapnia, ensuring an adequate cardiac output by treating hypovolemia, controlling temperature in cases of hypothermia or hyperthermia, and establishing and maintaining electrolyte balance, especially to treat hypokalaemia or hyperkalaemia (often summarized as the “four Hs”) [25]. More demanding is the recognition of a tension pneumothorax, pericardial tamponade, a thromboembolism (of the pulmonary or coronary artery), and rare causes, such as toxins (analogously summarized as the “four Ts”). In a recent review paper on IHCA patients, the authors concluded hypoxia, acute coronary syndromes, hypovolemia, arrhythmias, infection, and heart failure as the most often encountered reasons for cardiac arrest [26], despite the last three causes not being captured by conventional “Hs or Ts”. While identification and correction of reversible causes remain a key factor in ALS management, there are situations in which optimal conventional measurements fail to achieve ROSC. In such refractory cases, advanced interventions may provide temporary circulatory support while the underlying cause is addressed.

With widespread access to AEDs, early defibrillation can be beneficial in shockable rhythms, and the population's awareness of the devices' existence and utility has led to higher survival rates in OHCA nowadays compared to previous years. Adequate treatment decreases CPR duration and enhances the chances of ROSC and neurological outcomes. However, the quality of CPR remains a significant concern. Multiple studies have shown that CPR, even when initiated, is often performed suboptimal, which can limit its effectiveness [27]. Therefore, an essential factor in successful resuscitation is the high quality of compression. Guidelines recommend a compression rate of 100-120 per minute and a depth of 5-6 cm to ensure adequate blood flow to vital organs, which can positively influence the outcome. Proper chest compressions have been associated with good cerebral perfusion pressure. A Chinese study using porcine models showed a direct relationship among chest compression quality, cerebral perfusion pressure, and neurological outcomes. Notably, the study found that even after 4 minutes of poor CPR, subsequent high-quality CPR by medical professionals could still improve the outcome [28]. Even with an experienced medical team, fatigue can impair compression quality, potentially affecting the outcome. To address this, mechanical chest compression devices, such as the Lund University Cardiopulmonary Assist System device or Zoll AutoPulse®, provide compressions at standard depth and frequency, without any decline in performance. A retrospective analysis of the German Resuscitation Registry reported an increase in the ROSC rate when mechanical CPR was performed [29]. Meanwhile, a meta-analysis of randomized controlled trials comparing manual CPR with mechanical chest compression has not demonstrated a clear superiority of mechanical devices when used routinely in OHCA. Benefits were observed in challenging scenarios, such as patient transport, or when used as a bridge to advanced therapies, such as extracorporeal membrane oxygenation [30].

A newly adopted practice in ALS is the use of extracorporeal CPR via veno-arterial extracorporeal membrane oxygenation to provide circulatory support. This is considered a rescue therapy in younger patients with no significant comorbidities for whom conventional CPR is unsuccessful, and ROSC has not been achieved. Extracorporeal CPR is a solution when the cause of cardiac arrest needs more time to be found and resolved while maintaining adequate perfusion of the vital organs and brain. When applied to a population with fewer comorbidities, studies in this field showed better survival and neurological outcomes in patients treated with extracorporeal membrane oxygenation in the IHCA cohort [31]. Similar results were also registered in the OHCA collective, but the selection criteria can strongly influence the outcome. However, in the recent ECLS-SHOCK trial, which included 417 patients with OHCA and post-arrest cardiogenic shock, rescue therapy with extracorporeal Life Support did not improve survival in acute myocardial infarction-induced

shock, questioning the effectiveness of extracorporeal membrane oxygenation in refractory CPR.

1.3 Cardiac arrest characteristics

Every patient suffering from cardiac arrest presents traits that improve or worsen their chance of survival. Some of these factors are directly related to their person while others are related to the specific nature of the cardiac arrest event. This subchapter will guide on protective and dangerous factors in CPR.

Age, gender, and body mass index are personal factors. Cardiac arrest primarily affects older adults [32], and, conversely, increasing age has been associated with lower survival and worse neurological outcomes. However, recent advancements in the chain of survival, including early defibrillation and better post-cardiac arrest care, have led to better outcomes in elderly patients [33], but they remain lower than the rates observed in the younger population, with approximately 28.5% for IHCA and 11.1% for OHCA [32]. Encouragingly, recent studies have reported that among elderly patients who survive, many experience a favourable neurological outcome [34]. Older age is related to comorbidities, which can affect the incidence and severity of cardiac arrests. Pre-existing diseases such as coronary artery disease, congestive heart failure, structural heart conditions, and prior episodes of arrhythmia enhance the risk of cardiac arrest and also worsen the outcomes after suffering one. The conventional cardiovascular risk factors, including smoking, hyperlipidemia, diabetes, anemia, kidney diseases, and hypertension, further increase risk, underscoring the importance of preventive strategies in cardiovascular health.

Sex also plays a role; data from a long-term prospective study identified the male sex with a 3-fold higher risk of cardiac arrest occurrence [8]. This difference may partially be explained by a higher prevalence of coronary artery disease and lifestyle-associated risk factors among the men. Women tend to be older when they experience a cardiac arrest, are less likely to present a shockable rhythm, or receive bystander CPR, and overall have a lower survival rate. A recent Swedish study estimates a 30-day survival rate after OHCA of 6.2% in women compared to 10.7% in men [35]. Despite this, there was no difference in neurological outcome between genders after ROSC. Previous reports have shown that higher BMI is associated with worse survival. This is perhaps due to prolonged resuscitation [36] and challenging CPR techniques to perform in obese patients, where the conventional compressions would not suffice to simulate cardiac beats [37].

Cardiac arrest characteristics are the initial findings in management and also influence outcomes. The initial electrocardiographic rhythm occurring at the beginning of a cardiac arrest can be classified as either shockable or non-shockable. The distinction is essential

for therapy. Asystole, defined as a flatline on the ECG, and pulseless electrical activity (PEA), which is basically any electrical activity without the necessary output to generate a peripheral pulse, are non-shockable rhythms. For these, no intervention on the elective heart axis is helpful during resuscitation; only pharmacological interventions are possible. Ventricular tachycardia (VT) and ventricular fibrillation (VF) are shockable rhythms. These benefit from fast defibrillation and have a better survival chance [6, 7]. However, they do not appear equally in both types of cardiac arrest and in both genders. In IHCA, more than 80% of the cases involve non-shockable rhythms, which are associated with higher mortality than shockable rhythms [8]. As described previously, women have a less common shockable rhythm than men [38].

Other factors that can influence the outcome in the case of a cardiac arrest are the time from the development of cardiac arrest to the first attempted CPR. Any form of cardiac arrest is characterized by a cessation of cardiac activity and impairment of systemic circulation, resulting in global oxygen deprivation. Chest compressions mimic the heart's activity and allow a minimal flow (referred to in the literature as low-flow time) to high-oxygen-consumption organs, such as the brain. No-flow time (NFT) and low-flow time (LFT) are crucial factors in the survival and outcomes of cardiac arrest. Multiple studies have shown that increased NFT is associated with worse survival and neurological outcome. A recent study showed that survival in a collective of cardiac arrest without CPR being performed by a bystander was 11 % and only 8% survive with a favorable neurological outcome [39]. With every minute without CPR, the probability of survival with a good neurological outcome decreases by 13% [33]. Therefore, the NFT plays a crucial role in resuscitation, with particularly unfavorable outcomes when the duration exceeds 10 minutes. A recent study conducted in Japan showed that prolonged NFT increases the proportion of patients who convert from a shockable to a non-shockable rhythm. Regarding the LFT, the same Japanese study showed that CPR performed beyond 15 minutes increases the probability of conversion to non-shockable rhythms [40].

Survival following OHCA can be significantly influenced by bystander CPR, which reduces no-flow time. In Europe, the annual incidence of OHCA ranges between 67-170/100.000 inhabitants. According to the EuReCa register, bystander CPR is performed in approximately 58% of cases, with a notable variability between countries, ranging from 83% in Norway to just 13% in Serbia [4]. A systematic meta-analysis of 37 publications over the past 20 years has confirmed the benefits of layperson-initiated CPR, showing improved recovery outcomes and reduced intensive care unit admission rates [41]. The European trend nowadays is to promote early recognition of a cardiac arrest and the timely use of CPR and AEDs, particularly through training programs in schools and public institutions. While the relationship between CPR duration and survival remains inconclusive, several

factors, such as the patient's age, cardiac rhythm, and most importantly NFT, must be considered when deciding whether to terminate resuscitation efforts or to escalate to advanced resuscitation techniques[42].

Interestingly, the geographic and social context of cardiac arrest onset influences outcomes. For instance, occurrences in metropolitan areas have been associated with better survival rates and outcomes than in rural regions [43]. Moreover, disparities in CPR delivery are evident across racial and ethnic groups. A US-based study found that white individuals are more likely to receive bystander CPR at home (47.4%) compared to the Hispanic and Black populations (38.5%) [44]. These differences are thought to be linked to unequal access to CPR training. Similar disparities are observed when cardiac arrest occurs in public spaces, suggesting a systemic pattern. Many of these factors are interconnected. For instance, when a bystander witnesses cardiac arrest, timely intervention, especially in societies where BLS training is available, can significantly reduce NFT and improve outcomes. Bystanders can also inform medical personnel about the ability to provide timely, adequate treatment, for instance, for the initial heart rhythm. The chance of survival increases when cardiac arrest is witnessed, and CPR is started before the arrival of the EMS. Alerting EMS and immediately implementing ACLS can improve survival.

1.4 Post-resuscitation management

From a clinical viewpoint, once ROSC is established, the primary objective is to stabilize the patient and identify and treat the underlying cause of the initial CA. In addition, a series of interventions must be undertaken to optimize the compromised cardiovascular system. The four main pillars are blood pressure, oxygenation, and temperature regulation, coronary angiography with percutaneous coronary intervention, and, in some cases, protected by mechanical circulatory support. This subchapter provides a brief overview of current evidence-based recommendations in post-ROSC care.

Ensuring adequate oxygenation and effective carbon dioxide removal is crucial. Depending on the patient's neurological status and hemodynamic stability, endotracheal intubation may be necessary. Guidelines recommend maintaining spontaneous respiration in patients after a short period of cardiac arrest and ROSC, while patients who remain comatose after ROSC should be intubated. Current guidelines emphasise the importance of maintaining normocapnia, avoiding both hypoxemia and hyperoxia [45]. Controlled oxygen delivery, either via mechanical ventilation or spontaneous breathing, aims to prevent the formation of superoxide radicals and further tissue damage by providing only the required amount of oxygen. In the early post-cardiac arrest phase, elevated CO_2 is often

indicative of impaired tissue perfusion and hyperventilation. CO_2 is a critical regulator of vascular tone, particularly in cerebral circulation. Hypercapnia induces cerebral vasodilatation and increases cerebral blood flow, whereas hypocapnia leads to vasoconstriction, potentially reducing cerebral blood flow and increasing the risk of cerebral ischemia [45, 46]. Current guidelines report insufficient evidence to favour mild hypercapnia over normocapnia after ROSC [45]. However, a pilot study compared NSE levels between hypercapnic and normocapnic groups, suggesting that elevated CO_2 levels may be associated with poorer neurological outcomes [47].

In the majority of OHCA, the underlying aetiology is cardiac, most commonly acute myocardial ischaemia. Numerous observational studies conducted over recent years have demonstrated a significant association between early percutaneous coronary intervention (PCI) and improved survival and better neurological outcomes in OHCA patients [7]. However, identifying which of the resuscitated patients will benefit most from this intervention remains a clinical challenge. ST elevations on ECG following ROSC are essential when considering coronary angiography. Patients without ECG elevations benefit from a conservative approach focusing on hemodynamically stabilisation, as early catheterisation has not shown a clear benefit in this subgroup [48]. Physicians might follow, in these cases, the acute coronary syndrome algorithm and determine troponin levels to diagnose non-ST-elevation myocardial infarction. However, several studies have shown no significant difference in survival or neurological outcomes among NSTEMI patients who received either early or delayed PCI. In post-ROSC ECGs, patients who show an ST-elevation or a left bundle branch block are found to have a coronary lesion in more than 80% of the cases [49]. Patients with ST-segment elevations should receive catheterization directly after hemodynamic stabilisation.

Given the improvements in survival rates for IHCA and OHCA over the last decades, greater attention has been paid to the pathophysiology of cardiac arrest and the metabolic changes that occur during and after ROSC, which can influence survival. Post-cardiac arrest syndrome is associated with a deranged pathophysiology, with important changes in the respiratory and cardiovascular systems. Cardiac arrest results in inadequate oxygen delivery below the cellular mitochondrial threshold, leading to metabolic acidosis and cellular destruction. The acid-base disturbance interacts with endogenous catecholamine release, reducing the myocardial response to catecholamines and resulting in reduced contractility, further hypoperfusion, and cellular damage. Consequently, post-cardiac arrest myocardial dysfunction is usually associated with a low cardiac index and often necessitates the use of a vasopressor to maintain adequate perfusion. A Cochrane review analysing multiple RCTs found no significant difference in mortality outcomes among various vasopressors [50]. The choice of vasopressors is based on current guidelines, taking into

account the biventricular ejection fraction and right atrial oxygen saturation. Noradrenaline is often preferred for its efficiency and lower arrhythmogenic potential. In cases of myocardial dysfunction, dobutamine is often used for its ability to increase cardiac output. However, findings from the Neuroprotective trial indicate that while it improved cardiac index, it does not appear to mitigate neurological injury [51]. Management of mean arterial pressure (MAP) is critical in post-resuscitation care. While hypotension (MAP <65mmHg) is associated with poor outcome, targeting higher MAP (80-100mmHg) has not consistently demonstrated additional neurological benefit [52]. A few observational studies suggest an optimal MAP around 80-100 mmHg may improve cerebral oxygenation and outcomes, especially when elevated intracranial pressure is expected. Therefore, the current recommendation focuses on avoiding hypotension and tailoring MAP targets to individual patient needs, guided by indicators such as urine output and lactate levels. As a determinant of cardiac index, heart rate may influence outcome after cardiac arrest, with bradycardia (30-40 bpm) associated with better long-term outcomes in both hypothermia-treated and non-targeted temperature control groups [53]. Post-cardiac arrest syndrome shares pathophysiological features with septic shock, and several randomized controlled trials have evaluated the role of steroids in comatose survivors. However, did not demonstrate a significant benefit in outcomes, hemodynamic, or end-organ failure-free days; therefore, the current guideline recommends against its routine use.

For patients unresponsive to pharmacological intervention, a mechanical circulatory support device, such as Impella or ECMO, may be considered. However, recent retrospective studies have not demonstrated a consistent improvement in clinical outcomes with these devices [54]. However, mechanical circulatory support should be carefully considered in selected patients, particularly those with short cardiac arrest duration (<10 minutes), a Glasgow Coma Score>8 at hospital arrival, and evidence of ST elevation. Close monitoring of complications and adverse events remains essential [45].

The final phase of post-cardiac arrest management focuses on optimising neurological recovery by targeting temperature management. Induced hypothermia has long been considered neuroprotective, as it reduces the cerebral metabolic rate by approximately 6% for every 1°C decrease in core temperature [55]. According to the latest guidelines, it is weakly recommended to promptly induce mild hypothermia (32-32°C) for a minimum of 24 hours in patients who remain unresponsive after ROSC. This applies to IHCA cases with any initial rhythm, as well as OHCA cases with non-shockable rhythms, who remain unresponsive after ROSC [7]. During this cooling phase, adequate sedation and analgesia are necessary to prevent shivering and ensure patient comfort. Sedative medication should be selected to minimize cardiovascular depression and allow for later neurological assessment. Commonly used combinations include an opioid with a sedative agent. Recent

evidence, particularly from the TTM 2 trial, has questioned the benefit of hypothermia. This large multicentre randomized controlled trial compared targeted hypothermia (33°C) with targeted normothermia in unconscious patients after OHCA. The results showed no difference in mortality or favourable neurological outcomes between the two groups [56]. This has shifted guidelines and clinical practice toward actively avoiding fever rather than routinely inducing hypothermia [57], whereas data remains inconsistent. If the patient is mildly hypothermic after ROSC, they should not be actively warmed to achieve normothermia.

In the post-resuscitation phase, a series of neuroprognostic tests is typically performed on comatose patients, commonly at least 72 hours after the event, once normothermia has been achieved. A multimodal approach is recommended, including cerebral imaging (such as computer tomography or magnetic resonance imaging), serum biomarkers of neurological injury, detailed clinical neurological examination, and electroencephalography (EEG) to detect seizures or background activity. To improve the predictive value of neurological assessment, the ERC-ESIMC developed an algorithm for comatose patients beyond 72 hours, incorporating clinical examination, serum biomarker testing, and neuroimaging, as shown in Figure 2. The recent ERC-ESIMC 2025 algorithm combines this multimodal approach and integrates both favourable and unfavourable signs to improve the accuracy and reduce the number of indeterminate cases, providing a more individualized prediction of neurological outcome after cardiac arrest.

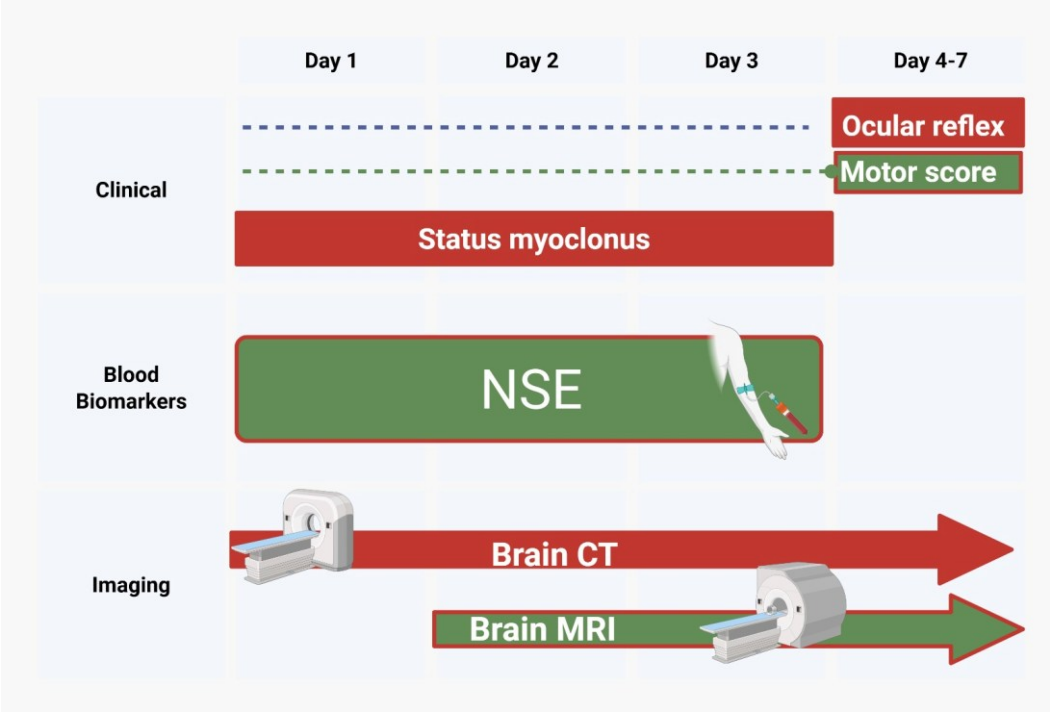

Fig. 2: Prognostic assessment algorithm ERC-ESIMIC 2025. CT = computed tomography; MRI = magnetic resonance imaging; NSE = neuron-specific enolase. Adapted after [18, 45]. This figure was created in BioRender.

1.5 Neurological prognostication

The critical post-cardiac arrest phase highlights the importance of neurological function prediction, as survivors may experience a variety of impairments in quality of life due to neurological injury. Neurological outcome is usually dichotomized in studies into good or poor, and several clinical scores have been developed to assess it systematically. These scales assess neuropsychiatric function and daily living abilities, with death included as the worst outcome.

The Cerebral Performance Category (CPC) is the most widely used scale for assessing neurological outcome at hospital discharge and was developed in the early 1980s as a refinement of the Glasgow Outcome Scale, with the primary aim of assessing cerebral function after brain injury. The CPC scale comprises five categories as seen in Table 1. It divides patients into good (CPC 1-2) and poor (CPC 3-4) neurological outcomes. CPC of 5 highlights deceased patients. Although CPC is the most commonly used scale, it has some limitations in discriminating between mild and moderate disability; therefore, the modified Rankin Score is preferred for measuring functional recovery [58].

The modified Rankin Scale has been used as a measure of global disability in stroke and brain injury [59], and shares some similarities with CPC, although its primary focus is on functional status. The modified Rankin Scale measures patients' independence on a scale from 0 to 6, as shown in Table 2. While CPC remains widely used to report neurological outcomes after cardiac arrest, the modified Rankin Scale has been recommended by the International Liaison Committee on Resuscitation as an alternative, offering finer discrimination of disability levels with comparable reliability in distinguishing good and poor neurological outcomes.

Cerebral Performance Category (CPC)

CPC 1	Good, intact cerebral performance: alert, conscious, able to work, minor sequelae possible.
CPC 2	Moderate cerebral disability: conscious, able to independently manage daily activities, neurological deficits are possible.
CPC 3	Severe cerebral disability: conscious but dependent on support from others for daily activities. Severe cognitive deficits possible,
CPC 4	Coma or vegetative state: unconscious and unaware of surrounding, no interaction with environment.
CPC 5	Death or brain death

Table 1. CPC score for quantification of neurological outcome. *Adapted after [60].*

Modified Rankin Scale (MRS)

0	No symptoms
1	No significant disability: able to carry out all usual duties and activities
2	Slight disability: unable to carry all previous activities, but able to look after own affairs without assistance
3	Moderate disability: require help but able to walk without assistance
4	Moderately severe disability: unable to walk and attend to bodily needs without assistance
5	Severe disability: bedridden, incontinent and require constant nursing care.
6	Dead

Table 2. MRS score for quantification of neurological outcome. *Adapted after [60].*

1.6 Prognostic markers after CPR

When addressing the topic of prognostication, a plethora of information is available on cardiac arrest traits (witnessed arrest, CPR duration, no-flow time, initial heart rhythm) and patients' characteristics (age, gender, comorbidities), which all contribute to the broader prognostic picture. Despite these, clinics have improved prognostication over the last few decades by incorporating laboratory parameters into their forecasts. Here, two different groups can be distinguished: biomarkers and parameters that can be routinely determined in the clinics, and biomarkers with scientific value, for which detailed laboratory methods, mainly experimental, are needed for determination. In addition, while several parameters have proven accurate in predicting both survival and neurologic development, other biomarkers are helpful only in one of these outcomes. In the following subchapter, the markers predicting mortality outcomes will be presented.

1.6.1 Markers for forecasting survival

Blood-based biomarkers have been widely investigated for their association with survival after cardiac arrest. Among these, serum lactate has received the most attention. Lactate accumulates during tissue hypoperfusion, mirroring an imbalance between metabolic demand and supply [61, 62]. Recent studies have found that in some life-threatening conditions, such as septic shock, lactate levels rise due to a hypermetabolic state, perhaps even independent of tissue hypoxia [63, 64]. Since both its production and clearance are influenced by multiple physiological mechanisms, interpreting elevated lactate levels and understanding why they have risen might prove clinically challenging [65]. Nonetheless, elevated serum lactate has been consistently associated with a higher mortality in critically ill patients [66]. Moreover, a slower rate of lactate clearance during the first hours of illness was associated with worse outcomes [67-69]. While many of these

findings stem from studies involving sepsis or septic shock, similar prognostic value has been observed in other types of shock, including cardiogenic shock. Measurement of lactate levels at hospital admission, as well as at 8 and 24 hours, along with lactate clearance metrics, has demonstrated prognostic accuracy for survival [70-74]. Therefore, its utility was extended to patients with cardiac arrest. Here, higher lactate during CPR or after ROSC forecasts a worse prognosis [75-77]. Interestingly, the lactate levels determined during CPR appear unrelated to the chance of ROSC [78]. In addition, lactate might help identify patients who would benefit from mechanical circulatory support [79].

In addition to lactate, procalcitonin, established initially as a marker of infection, has expanded its role to include outcome prediction in critically ill patients, including those resuscitated from cardiac arrest. Procalcitonin (PCT) is a precursor of the hormone calcitonin, which is released into circulation in response to pro-inflammatory cytokines and bacterial endotoxins [80]. Several studies have shown that elevated PCT levels following ROSC are associated with increased mortality and poor neurological outcomes [81, 82]. This association lies in the fact that postcardiac arrest syndrome shares pathophysiological similarities with sepsis, both of which involve a systemic inflammatory response and multiorgan dysfunction. In contrast to lactate, which primarily reflects circulatory and metabolic status, PCT may provide additional insight into the inflammatory component of cardiac arrest. One study showed that PCT levels increased within 2 hours of post-cardiac arrest and are strongly associated with poor neurological outcome [82].

Serum phosphate has recently gained attention as a potential biomarker for prognostic after cardiac arrest, owing to its association with ischaemia-reperfusion injury and microvascular dysfunction. Elevated phosphate levels are believed to reflect impaired microperfusion and loss of cellular integrity, thereby mirroring the severity of ischaemic injury. Several studies, including a large prospective cohort, have demonstrated that higher serum phosphate levels following resuscitation are associated with increased 30-day mortality. This association was observed in both IHCA and OHCA populations. Interestingly, among survivors with good neurological outcomes, the OHCA group tended to have lower phosphate levels compared to the IHCA group, suggesting that phosphate levels may also be related to neurological recovery [75]. Moreover, a study from south Korea found that in elderly cardiac arrest patients over 65 years, elevated phosphate levels are associated with poor neurological outcomes, further supporting the prognostic role of phosphate across different patient subgroups [83]. While further validation is required, these findings suggest that phosphate may serve as a useful, accessible biomarker to support early prognostication in cardiac arrest survival particularly for risk stratification regarding survival and neurological outcomes.

1.6.2 Markers for forecasting neurological prognostication

Two biomarkers have received significant scientific attention across multiple cardiac arrest collectives due to their prognostic value in stratifying neurological outcomes: neuron-specific enolase (NSE) and S-100 calcium-binding protein B (S-100B). Both are released into circulation following injury to neurons and glial cells and can be quantified in plasma using an enzyme-linked immunosorbent assay (ELISA) [84].

NSE, a neuron-specific isoform of the glycolytic enzyme enolase, is one of the most extensively studied biomarkers for assessing neurological outcome after cardiac arrest. Its plasma and cerebral fluid concentrations increase in response to brain injury from trauma, stroke, intracerebral haemorrhage, or hypoxic-ischaemic injury following CPR. However, elevated levels may also originate from extracerebral sources, such as haemolysis [45] or neuroendocrine tumours, leading to false-positive results [85]. Current clinical guidelines recommend serial measurement of NSE at 24h, 48h, and 72h post-cardiac arrest to evaluate the extent of neurological injury [45]. An NSE concentration extending 60µg/L at 48h and 72h is associated with poor neurological outcomes [45, 86]. With a half-life of 24h, NSE is thought to correlate positively with the extent of brain injury [85, 87], being independent of previously used sedatives [45] or post-cardiac arrest targeted management temperature, as demonstrated by a recent multicentre trial on OHCA collective [87].

S-100B, a member of the S-100 family of calcium-binding proteins, is predominantly produced by astrocytes and is released into the bloodstream when the blood-brain barrier is disrupted [88]. Persistent elevation over 24-72 hours after ROSC is indicative of irreversible brain damage and correlates with poor neurological outcomes [89]. Nevertheless, its specificity is limited, as elevated levels may also occur in the context of trauma, systemic inflammation, or extracranial injury [88]. High S100 levels are predictive of poor outcomes in OHCA [45, 89].

Emerging biomarkers are currently being evaluated for their prognostic value following a cardiac arrest. Among them, glial fibrillary acidic protein an intermediate filament found in astrocytic cytoskeleton and known for its role in predicting neurological outcome after head trauma. Another promising marker is the neurofilament light chain, a protein specifically expressed in neuronal axons. Similar to NSE, elevated blood levels of neurofilament light chain and glial fibrillary acidic protein reflect hypoxic-ischaemic brain injury. Both biomarkers have shown potential for strong prognostic performance, with neurofilament light chain appearing earlier in circulation and demonstrating superior predictive accuracy compared to NSE and glial fibrillary acidic protein [90, 91]. However, further validation in larger clinical studies is required before these biomarkers can be

implemented in routine practice. Currently, NSE remains the only biomarker recommended by international guidelines for neurological prognostication after cardiac arrest.

Tau protein, a marker of axonal injury, is not yet routinely used for neurological prognostics after cardiac arrest, but is considered a promising candidate. Plasma tau levels increase shortly after cardiac arrest and may remain elevated for several days, offering a potentially valuable prognostic window. However, tau protein lacks complete specificity for hypoxic-ischemic brain injury and may also be elevated in neurodegenerative diseases like Alzheimer's disease. When tested in a large prospective cohort study, elevated tau levels were associated with poor neurological outcome and shorter survival following cardiac arrest. The analysis also included NSE measurement and found that tau provided a more accurate prediction of poor neurological outcomes independent of TTM intervention [92].
MicroRNA (miRNA), although not yet implemented in routine clinical practice, present a novel class of biomarkers with potential prognostic utility in post-cardiac arrest management. Specific miRNAs are released in response to hypoxic-ischaemic injury and may reflect both neurological damage and the brain’s adaptive response. For example, miR-124 has been associated with neuronal death and poor outcomes, with elevated levels directly after the injury and further rising after 24-48 hours. miR-124 showed high specificity at 24h and 48h after cardiac arrest for the prognostication of poor neurological outcome (CPC 3-5) [93]. The study noted limitations due to the small patient sample but emphasized the promising value of miR-124 in predicting neurological outcome. Compared to conventional biomarkers, miRNAs offer greater molecular stability and insight into injury mechanisms. However, their clinical application is currently limited by the need for standardized detection methods and further validation in large-scale studies.

Given the limited specificity and sensitivity of any single biomarker, current guidelines do not recommend relying on biomarkers alone for prognostication after cardiac arrest. Instead, a multimodal approach that incorporates clinical examination, neuroimaging, and electrophysiological testing is advised to improve diagnostic accuracy and guide decision-making.

1.7 Aims

Accurate prediction of survival and neurological outcome after cardiac arrest remains a challenge, and currently, post-arrest prognostication lacks precision. Early and reliable prognostic tools are essential for guiding therapeutic decisions during and after CPR, avoiding futile interventions, and supporting communication with families. Currently, several prognostic scores show high prognostic accuracy, but they rely on complex parameters. In clinical practice, lactate levels are used for forecasting mortality, especially with very high levels showing a strong association with a higher mortality risk. For neuroprognostication, peak NSE levels 24–96 hours after ROSC have the highest diagnostic accuracy, but even these are often inaccurate, and determining the peak value can take several days. At the same time, prehospital blood gas analyses are increasingly available, making their diagnostic accuracy of special interest to emergency personnel and intensive care physicians.

Using a collective of non-traumatic cardiac arrest patients admitted to a tertiary German hospital, the current work's primary aim was to investigate the predictive value of arterial blood gas parameters, alone or in combination, collected initially during CPR, on in-hospital and 30-day mortality. Given the strong evidence supporting lactate's diagnostic accuracy as a biomarker following cardiac arrest, the current thesis aimed to identify potential improvements in its diagnostic capacity by integrating additional biomarkers derived from blood gas analysis.

The secondary aim was to assess the prognostic accuracy of neurological outcomes at hospital discharge, dichotomised as good or poor. The current thesis aimed to systematically assess the prognostic accuracy of each biomarker and, if applicable, identify combinations that enhance prognostic accuracy.

2 Methods and Materials

2.1 Study cohort

The relationship between laboratory parameters and outcomes was analysed in a cohort of patients suffering from cardiac arrest and subsequently treated in the non-traumatic intensive care units at a tertiary German hospital (University Clinic of Düsseldorf). Data were derived from 1086 patients who received CPR between 2013 and 2017.

Patients were included if they suffered from a non-traumatic cardiac arrest with the need for CPR and were admitted to the emergency department and/or non-traumatic intensive care unit of the University Clinic of Düsseldorf during or after the CPR. Patients were excluded from data collection if there were visible signs of body trauma acting as cause for the cardiac arrest. Also, patients aged <18 years were excluded from analyses. Only patients with available blood gas analysis were included in the analysis.

Data collection has been performed previously with prior approval by the ethics committee of the Heinrich-Heine University Düsseldorf (2018-109-RetroDEuA). Due to the retrospective nature of the study, informed consent was waived by the ethics committee. The current work represents a secondary analysis of a pre-existing database of the working group of PD Dr. Erkens.

2.2 Collection of data

Data collection was performed from digital medical records stored in the University Clinic of Düsseldorf's hospital information system using the Medico and Cerner Deutschland GmbH programs. The data were extracted from several clinical sources, which were prehospital care protocols, physicians' and nurses' notes from the observational chart, clinical examination reports, medical letters, and laboratory results. All collected data was verified for accuracy and completeness before analysis. The database includes, among others, the following characteristics and variables:

- Baseline characteristics: age, gender, body mass index:
- Pre-existing comorbidities: summarized according to the organ system as cardiac, pulmonary, renal, or neurological disease
- Cardiac arrest characteristics: location (in-hospital versus out-of-hospital), initial heart rhythm (asystole, PEA, VT/VF, bradycardia)
- CPR characteristics: whether the cardiac arrest was witnessed, time to initiation of CPR, whether defibrillation was performed, and the number of defibrillations.
- CPR outcome: whether ROSC occurred
- Administered drugs: Adrenaline, antiarrhythmics drugs, vasopressors or inotropes.

- Initial arterial blood gas analysis (obtained at hospital admission for OHCA patients or during resuscitation for IHCA).
- Laboratory parameters (collected upon admission and daily during up to five hospitalisation days): electrolytes, renal function markers (serum creatinine and glomerular filtration rates), hemogram, CPR, NSE.
- Outcomes: mortality, discharge location, cerebral imaging (cerebral computer tomography or cerebral magnetic resonance imaging), and assessment of neurological function at hospital discharge (using the cerebral performance category).

2.3 Statistical analyses

Continuous data between two groups were tested using an unpaired t-test for normally distributed data and a Mann-Whitney test for non-normally distributed data; for three or more groups, data were tested using a one-way ANOVA. Normality for continuous data was assessed by D'Agostino and Pearson Test due to the larger expected sample size. The predictive value of single parameters was assessed using Receiver Operating Characteristic (ROC) curves, with accuracy approximated by the area under the ROC Curve. Confidence intervals were approximated using the Wilson/Braun Method. In some analyses of prognostically relevant markers, the cut-off was determined using the Youden Index, which maximizes sensitivity and specificity [94]. Independent associations between variables and mortality were assessed using (simple/multiple) logistic regression with survival to hospital discharge (binary variable) as the outcome variable, or Cox regression with monitoring days as the time variable, as mentioned. Adjustment was performed for lactate and for the individual traits of age, cardiac arrest type, and CPR duration. Age and CPR duration were included as continuous variables, whereas cardiac arrest type was analysed as a binary variable (OHCA versus IHCA). A comparison of logistic models was performed by Akaike´s Information Criterion for models with the same number of variables.

2.4 Software

Medical data were initially collected from the local hospital information system (Medico, Cerner Germany) and the digital archive (PEGASOS, Nexus/Marabu, Germany). Database handling was performed in Microsoft Excel 2021 (V. 16.55, Microsoft, Redmond, Washington, United States). Some figures were created in biorender.com (https://www.biorender.com). Statistical testing and graphical representation were performed in GraphPad Prism 9.3.0 (GraphPad Software, San Diego, CA, USA). Large language models were used for text editing.

3 Results

3.1 Baseline characteristics

In total, there were 1086 patients with non-traumatic cardiac arrest admitted to the University Hospital of Duesseldorf between 01.01.2013 and 31.12.2017. Of these, 742 patients had arterial blood gas analyses at hospital admission and were therefore included in the analyses. Figure 3 shows the flowchart for patient inclusion.

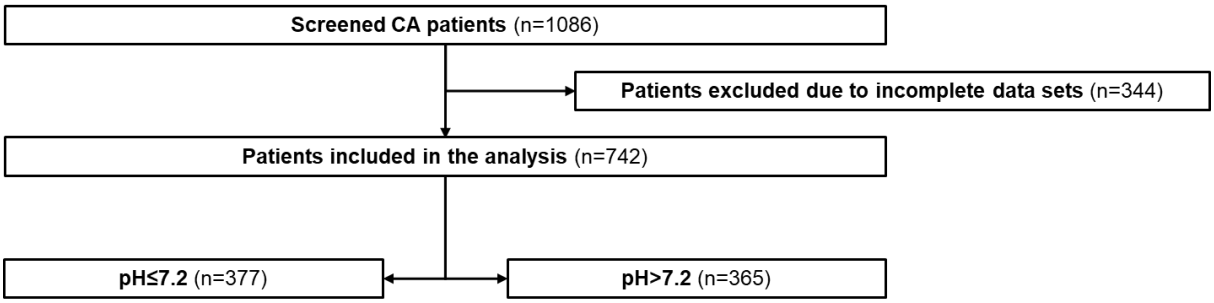

Fig. 3: Flow chart of the patient population. CA = cardiac arrest. Adapted after [95].

Patients had a mean age of 70 years and a male proportion of 63% (*n*=465). Approximately two-thirds of the cases involved ICHA (*n*=498), while one-third were OHCA patients (*n*=244). During the hospital stay, three-quarters of patients died (*n*=546), whereas one-quarter survived and were discharged (*n*=196). The mean duration of CPR was 33,8 minutes with a median of 25 minutes. Regarding initial cardiac rhythms, asystole was documented in 248 cases, pulseless electrical activity (PEA) in 146 cases, ventricular fibrillation in 164 cases, and in 31 cases, bradycardia. In 153 cases, initial rhythms were not documented. Among the patients with ventricular fibrillation, 153 received defibrillation with an average of 4.2 shocks/ patient. A cardiac aetiology was identified as the cause of cardiac arrest in 37% of cases (*n*=277).

In total, 577 collapses were witnessed, while 101 were not witnessed. In 64 cases, this information was not available from initial reports. ROSC was achieved in 581 patients. An overview of the baseline characteristics of the entire collective is provided in Table 3.

Of the total study population, 196 patients (26.4%) survived to hospital discharge. Neurological outcome was assessed using the Cerebral Performance Category (CPC) score. Among survivors, 27 patients (13.8%) had a CPC I, indicating good cerebral performance, while 10 (5.1%) patients had a CPC II, consistent with moderate neurological disability. A total of 108 patients (55.1%) were discharged with CPC III, representing severe neurological impairment, and 17 patients (8.7%) with CPC IV, reflecting a comatose or vegetative state. In 35 cases (4.71% of the entire dataset), CPC data at discharge were not available. Although classified under the CPC system, 545 patients (73.45%) were recorded

with a CPC V score, representing brain death or death. Cerebral imaging was performed in 231 cases, and 43 of those showed evidence of cerebral injury. Measurement of neurological prognostic biomarkers (NSE) was performed in 248 patients, with a second determination at 24h in 232 patients. Table 4 summarizes the neurological outcomes of patients who survived cardiac arrest.

Demographics

Parameter	Entire collective
n	742
Age [y] (mean)	70
Gender [male] n, (%)	465 (63)
Witnessed arrest n, (%)	577 (78)
Bystander CPR n, (%)	69 (9)
CA cause n, (%)	
Cardiac cause	277 (37)
Other cause	465 (63)
CPR duration [min] (mean)	33.8
Location of cardiac arrest n, (%)	
IHCA	478 (67)
OHCA	244 (33)
Initial heart rhythm n, (%)	
asystole	248 (33)
PEA	146 (20)
VT/VF	64 (22)
bradycardia	31 (4)
unknown	153 (21)
Return of spontaneous circulation n, (%)	581 (78)
Pre-existing illness n, (%)	
Cardiac disease	453 (61)
Pulmonary disease	43 (6)
Renal disease	26 (4)
Neurological disease	48 (6)
Malignancy	46 (6)
Others	126 (17)
Coronary intervention after CPR n, (%)	174 (24)

Table 3: Baseline, cardiac arrest and CPR characteristics, and pre-existing diseases. *Abbreviations: y = years, CPR = cardiopulmonary resuscitation, CA = cardiac arrest, PEA = pulseless electric activity, VT = ventricular tachycardia, VF = ventricular fibrillation. Some parts of this table were previously shown in adapted form in [95].*

The initial arterial blood gas analysis, shown in Table 5, revealed a pH of 7.16 with a lactate level of 9.63 mmol/L, low bicarbonate levels, and a negative base excess, confirming a significant metabolic acidosis. Oxygenation was good, likely due to supplemental oxygen, but oxygen saturation was suboptimal, suggesting impaired oxygen utilization. It also reveals a mild hypercapnia and slightly elevated potassium levels.

Neurological outcomes

Outcome	Number	% of total
Survival	196	26
CPC at discharge		
CPC I	27	4
CPC II	10	1
CPC III	108	15
CPC IV	17	2
CPC V	545	73
Unknown	35	5
Cerebral imaging performed	231	31
Cerebral injury	43	19
NSE initial	248	33

Table 4: Neurological outcome at discharge. *Abbreviations: CPC = cerebral performance category; NSE = neuron-specific enolase. Some parts of this table were previously shown in adapted form in [95].*

Initial arterial blood gas analysis

Laboratory parameter	Unit	Median
pO2	mmHg	181.98
SaO2	%	91.02
pCO2	mmHg	49.84
pH	-	7.16
HCO3	mmol/L	17.30
BE	-	-9.2
Lactate	mmol/L	9.63
Na	mmol/L	146.85
K	mmol/L	4.98

Table 5: Initial arterial blood gas analysis of the cardiac arrest patients. *Abbreviations: pO_2 = partial pressure of oxygen, SaO_2 = arterial oxygen saturation, pCO_2 = partial pressure of carbon dioxide, HCO_3^- = bicarbonate, BE = base excess, Lactate = blood lactate concentration, Na = sodium, K = potassium. Some parts of this table were previously shown in adapted form in [95].*

Initial laboratory results at hospital admission are summarized in Table 4. The data represent the median values of key biochemical and haematological parameters across all included patients. Notable findings include elevated levels of troponin, LDH, and transaminases, suggesting widespread tissue damage. The median GFR was 47.95 mL/min/1.73m^2, indicating impaired renal function. Inflammatory markers such as CPR and PCT were moderately elevated, with median values of 5.47 mg/L and 3.29 ng/ml, respectively.

Initial laboratory parameters

Laboratory Parameter	Unit	Median
Na	mmol/L	147.28
K	mmol/L	4.89
Ca	mmol/L	2.19
Phosphate	mmol/L	2.29
Creatine	mg/dL	1.94
GFR	mL/min/1.73m^2	47.95
CRP	mg/L	5.47
PCT	ng/ml	3.29
Bilirubin	mg/dl	0.92
LDH	U/L	1108.75
GOT	U/L	602.28
GPT	U/L	325.76
GGT	U/L	96.74
Albumin	g/dL	2.93
NSE	ng/ml	63.08
WBC	x10^9/L	16.58
ERY	x10^9/L	3.66
HB	g/dL	10.75
HKT	%	33.34
THROMB	x10^9/L	206.38
QUICK	%	52.12
INR	-	2.05
PTT	sec	68.29

Table 6: Initial laboratory parameters in cardiac arrest patients. *Na = sodium; K = potassium; Ca = calcium, GFR = glomerular filtration rate; CRP = C-reactive protein; PCT = procalcitonin; LDH = lactate dehydrogenase; GOT = glutamate-oxaloacetate transaminase; GPT = glutamate-pyruvate transaminase; GGT = gamma-glutamyl transferase; NSE = neuron-specific enolase; WBC = white blood cell count; ERY = erythrocytes; HB = hemoglobin; HKT = hematocrit; THROMB =*

thrombocytes; INR = international normalized ratio; PTT = partial thromboplastin time. Some parts of this table were previously shown in adapted form in [95].

3.2 The prognostic value of blood gas parameters on mortality

To visualize the relationship between biomarkers from the first arterial blood gas analysis and in-hospital mortality, the distributions of survivors and non-survivors across ordered absolute values of the biomarkers were plotted and tested for monotonic trends (χ^2 test for trend). These analyses are shown in Figure 4. Two patterns emerged: First, some markers showed clear dose–response gradients: lower pH, higher lactate, lower bicarbonate, and more negative base excess were each associated with progressively higher mortality (all $p<0.0001$). Second, some variables exhibited non-linear associations, with the lowest mortality in mid-range values and higher mortality at both extremes, most evident for partial O_2 pressure (paO_2) ($p\approx0.002$) and potassium ($p<0.0001$). In contrast, partial CO_2 pressure ($paCO_2$) and sodium showed no consistent trend with survival ($p=0.16$ and $p=0.34$, respectively).

To further assess prognostic relevance, a biomarker comparison between survivors and non-survivors was conducted, and univariable ROC curves were constructed for in-hospital mortality. Because these analyses were exploratory, ROC curves were generated for all biomarkers, including those without a clear categorical trend in the previous analyses. These are collectively summarized in Figure 5.

A small but significant trend was visible for paO_2. Survivors had slightly higher paO_2 levels than non-survivors (192±140 versus 176±143 mmHg; Mann-Whitney test, $p=0.0167$). Among patients with very low paO_2 levels (e.g., <50 mmHg), there were almost no survivors (Fig. 4). Conversely, paO_2 levels showed little to no predictive accuracy in discriminating survivors of hospital stay (AUC 0.56, 95% Confidence interval: 0.51–0.60, $p=0.0167$, Fig. 5A).

Similar to paO_2, there was only a slight difference in $paCO_2$ (Survivors: 46±21 versus non-survivors: 51±25 mmHg, Mann-Whitney test, $p=0.0028$). While there were almost no survivors among cardiac arrest patients with initial $paCO_2$ levels between 61 – 90 mmHg, there was a more equal distribution in survival status for patients with initial $paCO_2$ levels over 91 mmHg (Fig. 4). In line with paO_2, the ROC curve of $paCO_2$ showed little to none predictive accuracy in discriminating survivors of hospital stay (AUC 0.57, 95% Confidence interval: 0.52–0.62, $p=0.0028$, Fig. 5B).

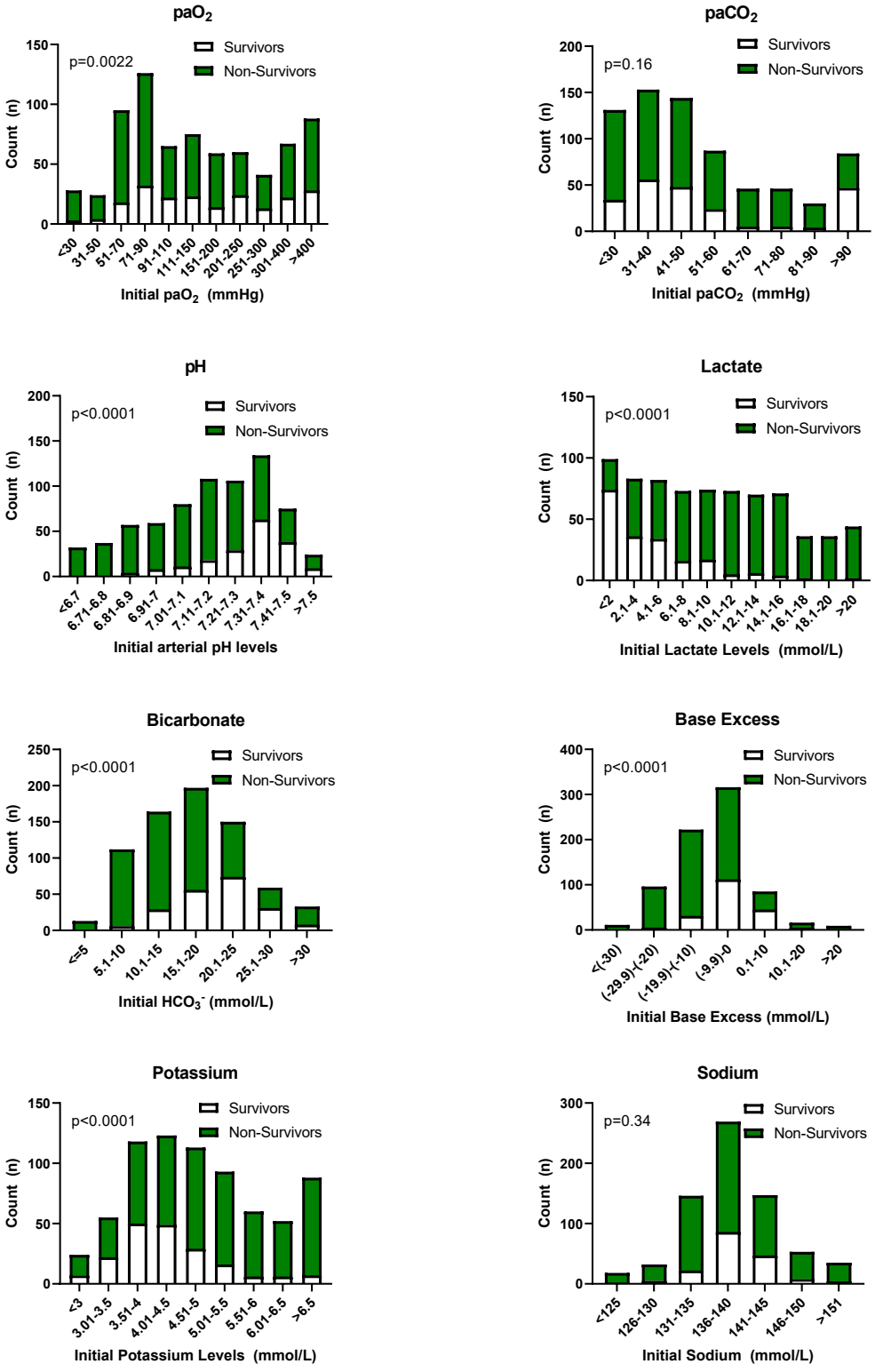

Fig. 4. Distribution of blood-gas and electrolyte values from the first arterial blood gas analysis by survival status. Bars show patient counts within predefined categories; white indicates survivors and green non-survivors. paO_2 = partial pressure of arterial oxygen; $paCO_2$ = partial pressure of arterial carbon dioxide. p-values refer to tests for trend across ordered categories.

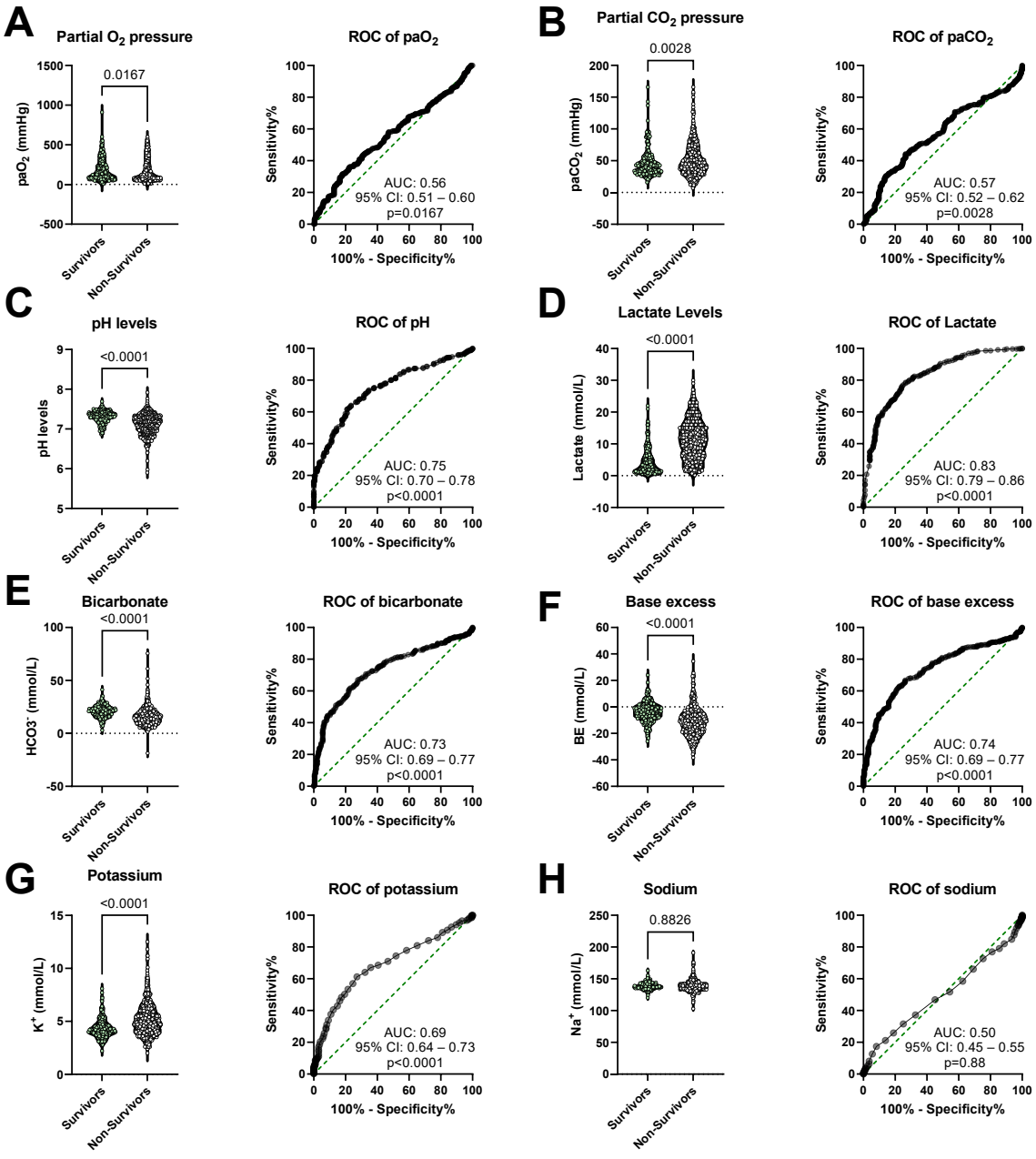

Fig. 5: Association between standard biomarkers from the first available blood gas analysis with in-hospital mortality: (A) Comparison of initial paO_2 between survivors and non-survivors (tested by Mann–Whitney U test, p=0.0167) and the corresponding ROC curve to predict in-hospital mortality (AUC=0.65% CI 0.51–0.6, p=0.0167); **(B)** Comparison of initial $paCO_2$ between survivors and non-survivors (tested by Mann–Whitney U test, p=0.0028) and the corresponding ROC curve to predict in-hospital mortality (AUC=0.57% CI 0.52–0.62, p=0.0028); **(C)** Comparison of initial pH levels between survivors and non-survivors (tested by Mann–Whitney U test, p<0.0001) and the corresponding ROC curve to predict in-hospital mortality (AUC = 0.75, 95% CI: 0.71–0.78. p<0.0001); **(D)** Comparison of initial serum lactate between survivors and non-survivors (tested by Mann–Whitney U test, p<0.001) and the corresponding ROC curve to predict in-hospital mortality (AUC=0.83% CI 0.79–0.86, p<0.001); **(E)** Comparison of initial bicarbonate levels between survivors

and non-survivors (tested by Mann–Whitney U test, p<0.001) and the corresponding ROC curve to predict in-hospital mortality (AUC=0.73% CI 0.69–0.77, p<0.001); **(F)** Comparison of initial base excess between survivors and non-survivors (tested by Mann–Whitney U test, p<0.001) and the corresponding ROC curve to predict in-hospital mortality (AUC=0.74% CI 0.69–0.77, p<0.001); **(G)** Comparison of initial potassium levels between survivors and non-survivors (tested by Mann–Whitney U test, p<0.001) and the corresponding ROC curve to predict in-hospital mortality (AUC=0.69% CI 0.64–0.73, p<0.001); **(H)** Comparison of initial sodium levels between survivors and non-survivors (tested by Mann–Whitney U test, p=0.88) and the corresponding ROC curve to predict in-hospital mortality (AUC=0.50% CI 0.45–0.55, p=0.88). Some parts of this figure were previously shown in adapted form in [95].

When observing the proportions of survivors and non-survivors across initial pH levels, there was a clear trend of increasing survivorship with higher pH. Whilst there were virtually no survivors in pH levels < 6,9, their proportion rose to almost half in pH levels between 7,31 – 7,4 (Fig. 4). Moreover, survivors had, on average, higher initial arterial pH levels compared to non-survivors (7.3±0.15 (SD) versus 7.1±0.25, Mann–Whitney U test, p<0.0001). As expected, pH showed high predictive accuracy in discriminating hospital survivors, reflected by an AUC of 0.75 (95% CI: 0.71 – 0.78, p<0.0001, Fig. 5C). The Youden Index for pH was 7.207, which was numerically very close to the clinically established cut-off for severe acidaemia at 7.2.

As with pH, there was a clear trend in survival proportions across lactate levels. Among patients with initial lactate levels < 2 mmol/L, more than half survived hospital discharge. With rising levels, rates of survival fell in an almost linear fashion with nearly no survivors among patients with initial lactate levels over 10.1 mmol/L (Fig. 4). In addition, survivors had, on average, 2.5-fold lower initial arterial lactate levels than non-survivors (4.6±4.2 versus 11.4±6.1 mmol/L; Mann–Whitney U test, p<0.0001). Similar to the current literature [68, 79, 96], lactate showed very high predictive accuracy in discriminating between survivors and non-survivors during hospital stay, with an AUC of 0.83 (95% Confidence interval: 0.79 – 0.86, p<0.0001, Fig. 5D). The Youden Index for lactate was 5.95 mmol/L.

For bicarbonate and base excess, the distributions of survivors and non-survivors across ordered absolute values showed a U-shaped trend, with nearly no survivors in patients with initial very low and very high values (p<0.0001 for trend for both biomarkers, Fig. 4). Survivors had, on average, slightly higher levels of bicarbonate compared with non-survivors (20.9±5.6 versus 16±8.1 mmol/L, Mann–Whitney U test, p<0.0001, Fig. 5E). The predictive accuracy in discriminating between survivors and non-survivors of hospital stay was moderate to high for bicarbonate, reflected by an AUC of 0.73 (95% Confidence interval: 0.69 – 0.77, p<0.0001). Similar to bicarbonate, the determination of base excess

differentiates between survivors and non-survivors, with a higher negative value registered in non-survivors ((-4.1)±7.4 versus (-11)±10.6 mmol/L, Mann–Whitney U test, p<0.0001, Fig. 5F). As bicarbonate, the predictive accuracy in discriminating hospital survivors was also moderate to high for base excess, reflected by an AUC of 0.74 (95% CI: 0.69 – 0.77, p<0.0001).

The analysis of electrolytes showed a skewed U-shaped pattern for potassium and a central U-shaped pattern for sodium. The survival rates were very low among patients with initially very high or very low electrolyte levels (Fig. 4). Conversely, there was a slight difference between potassium levels for groups (4.4±0.9 in survivors versus 5.2±1.5 mmol/L in non-survivors, Mann–Whitney U test, p<0.0001, Fig. 5 E). Potassium's predictive accuracy in discriminating survivors of hospital stay was low to moderate. (AUC 0.69, 95% Confidence interval: 0.65–0.73, p<0.0001). Compared to potassium, there was no significant difference between sodium levels (Survivors: 138.5±5.3 versus non-survivors: 138.9±8.3 mmol/L, Mann–Whitney U test, p=0.88), and, in line, no predictive accuracy in discriminating survivors of hospital stay (AUC 0.50, 95% Confidence interval: 0.46–0.55, p=0.88).

Collectively, these unadjusted distributions indicate that early metabolic derangement, particularly reflected in pH and lactate, but also bicarbonate and base excess tracks most strongly with mortality risk, while electrolytes are not particularly suitable to discern between cardiac arrest patients at risk.

3.3 Acidaemia predicts mortality irrespective of the aetiology

In initial analyses, the blood gas parameters with the highest prognostic accuracy in discriminating hospital survival were lactate and pH. Since lactate is a well-established marker for many intensive care conditions, cardiac arrest, and shock [63, 68, 70, 71, 76, 77, 79, 96-98], the current work focused on the prognostic capabilities of pH and its dependence on lactate.

In terms of etiology, acidemia can result from hypoperfusion (metabolic acidemia) or carbon dioxide retention (respiratory acidemia). This, along with the known association between lactate and lactic acidosis and mortality, raised the question of whether the prognostic relevance of acidemia for mortality was limited to specific circumstances. To answer this question, subgroup analyses of the predictive value of pH were performed by age, cardiac arrest duration, gender, type of cardiac arrest, and the two most common forms of acidemia. In addition, as proxies for the metabolic and respiratory origin, subgroup analyses were performed for different lactate and pCO_2 stratification groups. For all further

analyses, this work used the pH threshold of 7.2, which is clinically used for severe acidemia and was numerically very close to the Youden Index.

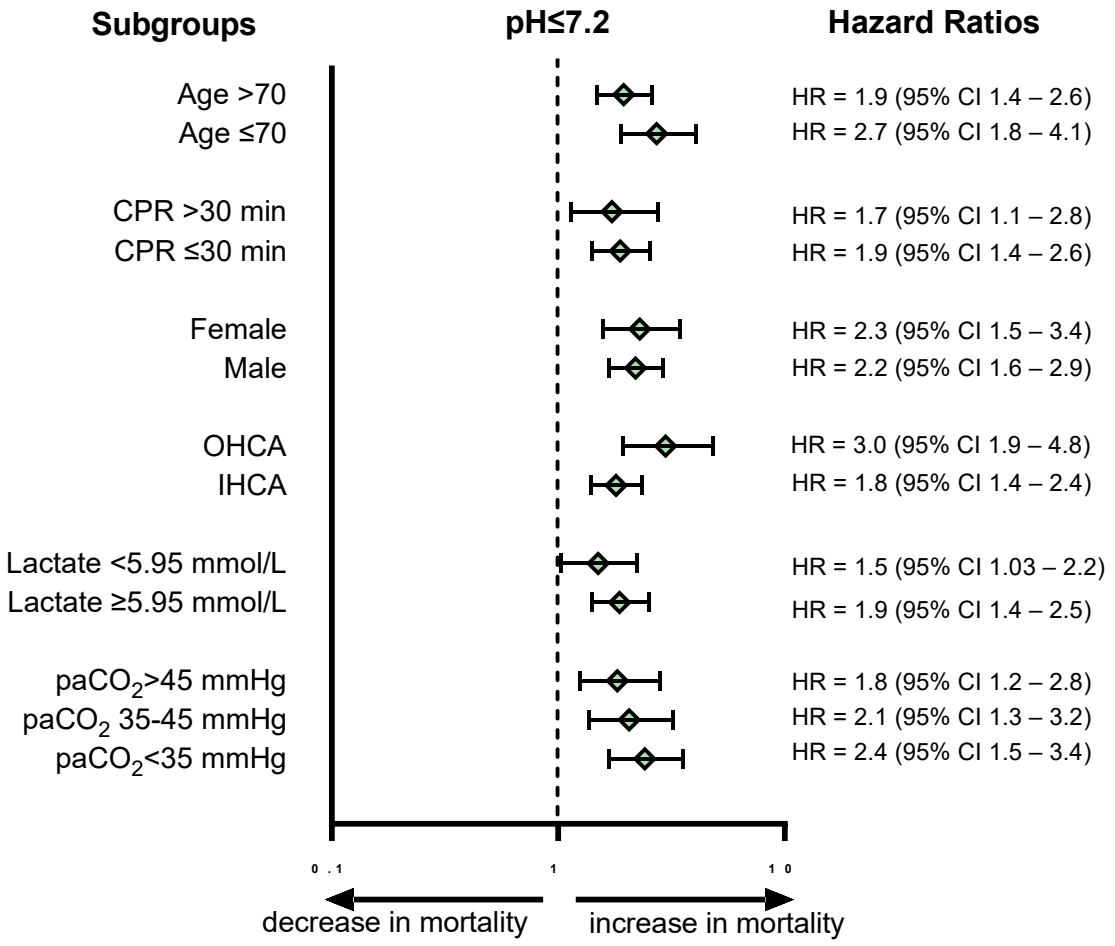

Fig. 6: Severe acidemia (pH ≤7.2) is associated with higher mortality across all analyzed subgroups. Hazard ratios (HRs) for mortality in patients with pH ≤7.2 across predefined clinical subgroups. Diamonds represent the point estimate of the HR, and horizontal lines indicate the 95% confidence intervals. Subgroups include age (>70 vs. ≤70 years), duration of CPR (>30 min vs. ≤30 min), sex, cardiac arrest location (out-of-hospital cardiac arrest [OHCA] vs. in-hospital cardiac arrest [IHCA]), lactate levels (<5.95 vs. ≥5.95 mmol/L), and arterial carbon dioxide pressure ($paCO_2$ >45, 35–45, or <35 mmHg). HRs >1 suggest increased mortality risk associated with acidemia (pH ≤7.2), while HRs <1 indicate a potential survival benefit. Figure adapted from [95].

As shown in Figure 6, pH ≤7.2 was associated with higher mortality across all subgroups, with HRs ranging from 1.5 to 3. Within this analysis, severe acidemia remained independently associated with in-hospital death after adjustment for lactate (as a proxy for systemic hypoperfusion) and $paCO_2$ (as a proxy for systemic ventilation), and resuscitation characteristics, indicating prognostic value regardless of the underlying cause of acidemia. To further assess the degree of interconnectivity between lactate and pH, correlation analyses were performed to determine whether lower pH levels were associated with higher

lactate levels. These are shown in Figure 7. By the R^2 of 0.38 ($p<0.0001$), the analysis showed only a mild to moderate relationship between pH and lactate.

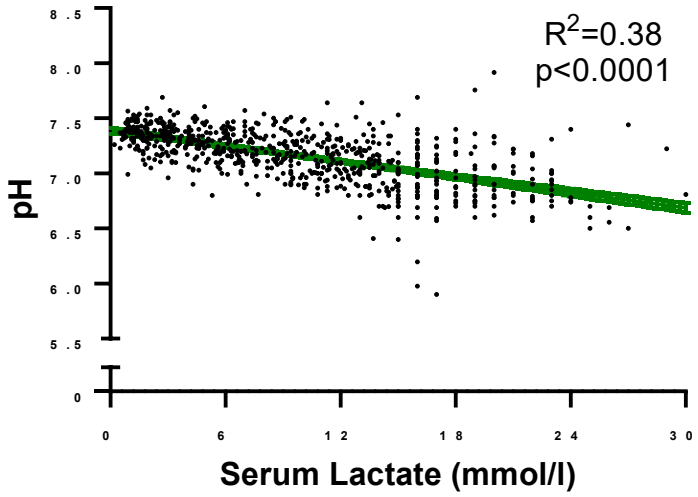

Fig. 7: Correlation analysis between lactate and pH. R^2 calculated by simple linear regression.

3.4 Acidaemia augments lactate's value in predicting short-term mortality

Since the previous analysis showed high predictive accuracy for pH and lactate, and the correlation analysis showed only mild collinearity, the question arose of whether pH might augment lactate levels in prognosticating survival. Therefore, the entire cardiac arrest group was stratified into four groups according to the previously calculated Youden indices (7.2 for pH and 5.95 mmol/L for lactate).

This stratification showed a more granular risk differentiation as shown by Figure 8. Cardiac arrest patients with high pH and low lactate levels had an in-hospital mortality of only 40%, compared to the 92% in-hospital mortality among patients with high lactate and low pH levels. As shown by the Kaplan-Meier analysis of the 30-day mortality, pH stratified further the risk of each lactate patient group, allowing an improvement in diagnostic accuracy of lactate for short-term mortality prediction.

A unit increase for pH showed an HR of 9-fold lower mortality chance (95% CI: 0.08–0.15, $p<0.0001$, Model 1) in the unadjusted analysis. The HR remained significant after adjusting for lactate (HR 0.29, 95% CI 0.19–0.42, $p<0.0001$, Model 2) and lactate, age, CPR duration, and type of cardiac arrest (HR 0.28, 95% CI 0.18–0.43, $p<0.0001$, Model 3).

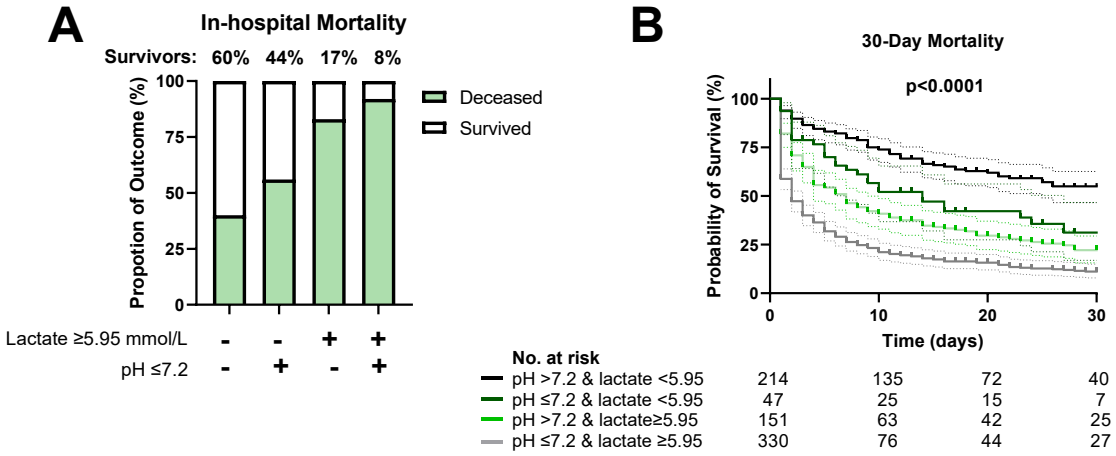

Fig. 8: Short-term mortality outcomes in cardiac arrest patients stratified into four groups by the Youden indices of pH and lactate. (A) Proportion of in-hospital survivors and non-survivors. (B) 30-day mortality in the Kaplan-Meier Analysis. P<0.0001 tested by Log-rank (Mantel-Cox) test. Some parts of this figure were previously shown in adapted form in [95].

Next, the results were corroborated in Cox regression analyses across several models to test the hazard ratio for pH level elevations, unadjusted (model 1), adjusted for lactate (model 2), and adjusted for lactate, CPR duration, age, and type of cardiac arrest (model 3).

Cox regression analyses with pH as a continuous variable

Variable	Hazard ratio	95% CI	p-value
Model 1			
pH [unit]	0.11	0.08 – 0.15	<0.0001
Model 2			
pH [unit]	0.29	0.19 – 0.42	<0.0001
Lactate levels [unit]	1.08	1.06 – 1.1	<0.0001
Model 3			
pH [unit]	0.28	0.18 – 0.43	<0.0001
Lactate levels [unit]	1.05	1.02 – 1.07	<0.0001
CPR duration [min]	1.02	1.01 – 1.03	<0.0001
Age [year]	1.03	1.01 – 1.04	<0.0001
Type of cardiac arrest [OHCA]	0.58	0.46 – 0.72	<0.0001

Table 7: COX regression analysis showing the HR of each pH unit increase associated with mortality to hospital discharge in unadjusted analysis (Model 1), after adjustment for lactate levels (Model 2), and after adjustment for lactate levels, CPR duration, age, and type of cardiac arrest (Model 3).

COX regression analyses were repeated with pH as a binary value with the previously established cut-off of 7.2. The results are shown in Table 8. This analysis showed that patients with a pH >7.2 were twice as likely to survive. After accounting for lactate, an initial pH >7.2 was associated with a 65% higher chance of survival. In line with model 3, adjusting the analysis for age, CPR duration, and type of cardiac arrest showed a 58% higher survival rate for pH >7.2, providing unequivocal evidence of the link between pH levels and survival, in addition to lactate dynamics.

Cox regression analyses with pH as a binary variable

Variable	Hazard ratio	95% CI	p-value
Model 4			
pH >7.2 [no]	2.21	1.78 – 2.78	<0.0001
Model 5			
pH >7.2 [no]	1.65	1.32 – 2.09	<0.0001
Lactate levels [unit]	1.1	1.08 – 1.12	<0.0001
Model 6			
pH >7.2 [no]	1.58	1.242 – 2.05	0.0003
Lactate levels [unit]	1.06	1.046 – 1.08	<0.0001
CPR duration [min]	1.02	1.013 – 1.02	<0.0001
Age [year]	1.02	1.016 – 1.03	<0.0001
Type of cardiac arrest [OHCA]	0.51	0.42 – 0.62	<0.0001

Table 8: COX regression analysis showing the HR of pH level >7.2 (as a binary value) associated with mortality to hospital discharge in unadjusted analysis (Model 4), after adjustment for lactate levels (Model 5), and after adjustment for lactate levels, CPR duration, age, and type of cardiac arrest (Model 6).

3.5 Base excess and bicarbonate are inferior to pH levels in augmenting the predictive value of lactate on mortality

In the initial analysis of blood gas variables, several parameters beyond pH and lactate proved prognostically relevant. These were bicarbonate, base excess, and potassium. To answer the question of which linked parameters would hold the highest accuracy, base excess and bicarbonate, whose AUROC proved superior to that of potassium in a previous analysis (Fig. 5), were included in the Cox regression analysis. Due to a high expected collinearity between pH, base excess, and bicarbonate, an analysis with two or three of these parameters was not considered valuable and was, therefore, not performed. Since model 3 in the previous Cox regression analyses showed the highest probability of being

correct, it was used, and the continuous variable pH was replaced by bicarbonate and base excess. The corresponding HR are shown in Table 9.

Cox regression analyses with BE & Bicarbonate as a continuous variable

	Model with BE			Model with Bicarbonate		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
BE / Bicarbonate [unit]	0.98	0.96–0.99	0.0005	0.99	0.97–0.99	0.048
Lactate levels [unit]	1.05	1.03–1.08	<0.0001	1.06	1.04–1.08	<0.0001
CPR duration [min]	1.02	1.01–1.02	<0.0001	1.02	1.01–1.02	<0.0001
Age [year]	1.03	1.01–1.03	<0.0001	1.02	1.01–1.03	<0.0001
Type of cardiac arrest [OHCA]	0.59	0.47–0.74	<0.0001	0.55	0.45–0.68	<0.0001

Table 9: COX regression analysis showing the HR of each base excess (left panel) and bicarbonate (right panel) unit increase associated with mortality to hospital after adjustment for lactate levels, CPR duration, age, and type of cardiac arrest.

Both variables showed a significant association with in-hospital mortality. Next, these models were compared to the one of pH as a continuous variable. Compared to the model including pH, the model including base excess showed a ΔAIC of -13, indicating that the model including pH levels would be strongly preferred. The calculated probability of being correct was 99.9% for the model including pH levels versus 0.1% for the model including base excess. Similarly, the comparison between the models with pH levels versus bicarbonate showed a ΔAIC of (-23.5), indicating that the model with pH levels would also be strongly preferred. Here, the probability of being correct was >99.99% for the model with pH levels versus <0.01% for the model with bicarbonate. Altogether, this shows that pH is superior to base excess or bicarbonate for mortality prognostication.

3.6 The prognostic value of blood gas parameters on neurological outcome among hospital survivors

The secondary aim of this thesis was to assess the prognostic accuracy of standard blood gas analysis variables on neurological outcome. Due to the high mortality of 73.6% in the cardiac arrest collective, further analyses were performed in the subgroup of hospital survivors, thereby excluding any patients with CPC V from further analyses. Exploratory analyses included a biomarker comparison between patients with CPC I–II (as proxies for good neurological outcome) versus CPC III–IV (as proxies for poor neurological outcomes), and univariable ROC curves were constructed for in-hospital mortality. These are collectively shown in Figure 9.

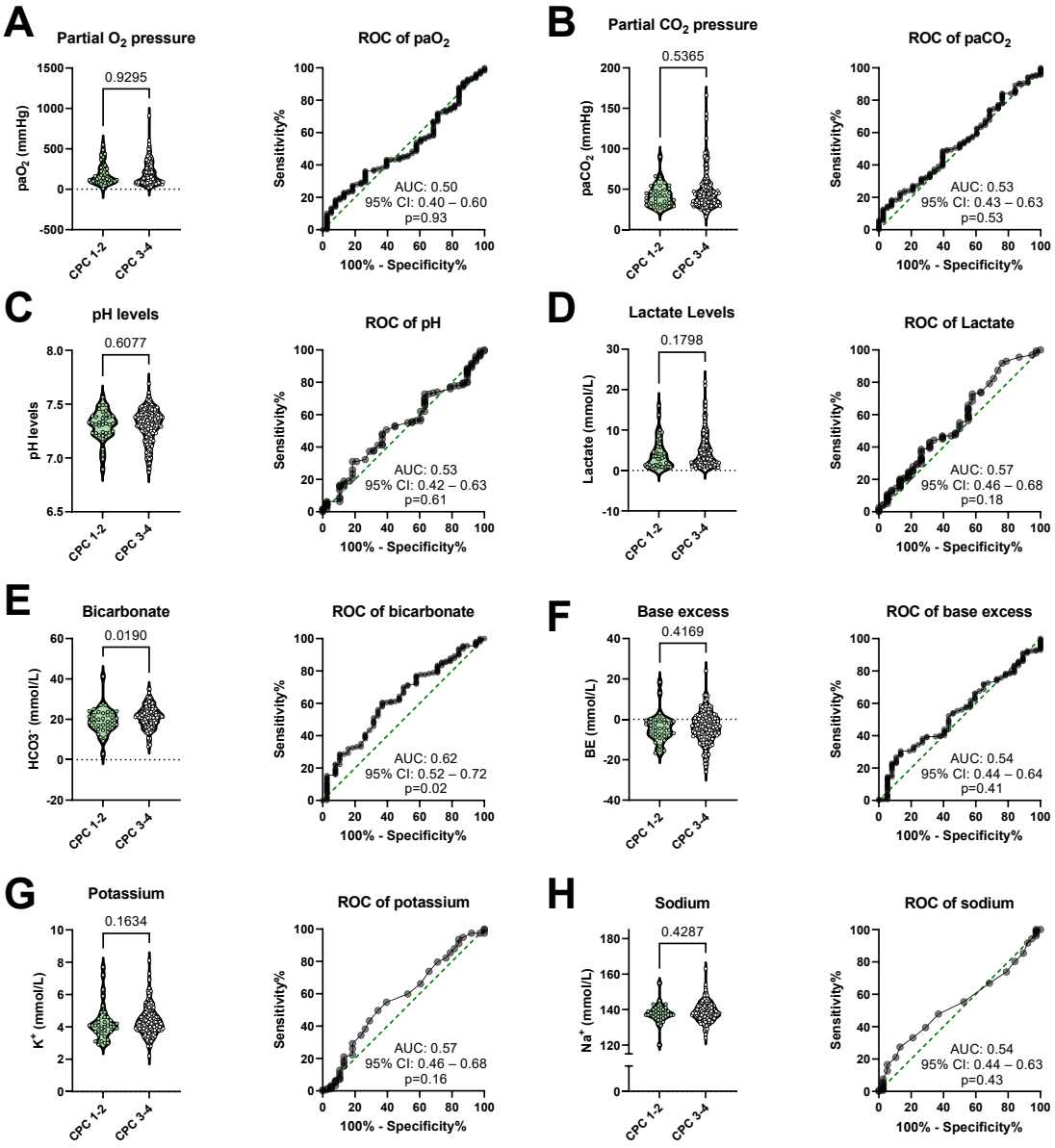

Fig. 9: Association between standard biomarkers from the first available blood gas analysis with neurological outcomes among hospital survivors: (A) Comparison of initial paO_2 levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.93) and the corresponding ROC curve to predict poor neurological outcomes (AUC=0.50% CI 0.4–0.6, p=0.93); **(B)** Comparison of initial $paCO_2$ levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.53) and the corresponding ROC curve to predict poor neurological outcomes (AUC=0.53% CI 0.43–0.63, p=0.53); **(C)** Comparison of initial pH levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.61) and the corresponding ROC curve to predict poor neurological outcomes (AUC = 0.53, CI: 0.42–0.63. p=0.61); **(D)** Comparison of initial lactate levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.18) and the corresponding ROC curve to predict poor neurological outcomes (AUC=0.57 CI

0.46–0.68, p=0.18); **(E)** Comparison of initial bicarbonate levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.02) and the corresponding ROC curve to predict poor neurological outcomes (AUC=0.62; CI 0.52–0.72, p=0.02); **(F)** Comparison of initial base excess levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.41) and the corresponding ROC curve to predict poor neurological outcomes (AUC=0.54; CI 0.44–0.64, p=0.41); **(G)** Comparison of initial potassium levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.16) and the corresponding ROC curve to predict poor neurological outcomes (AUC=0.57; CI 0.46–0.68, p=0.16); **(H)** Comparison of initial sodium levels between hospital survivors with good and poor neurological outcomes (tested by Mann–Whitney U test, p=0.43) and the corresponding ROC curve to predict poor neurological outcomes (AUC=0.54; CI 0.44–0.63, p=0.43). Some parts of this figure were previously shown in adapted form in [95].

Although oxygenation is crucial for cerebral metabolism, paO_2 levels showed slight variation between the two groups, with even higher values in the poor-outcome group (185 ± 133 vs. 193 ± 143 mmHg; Mann–Whitney U test, p=0.93). The predictive performance of paO_2 was negligible (AUC 0.50; 95% CI: 0.40–0.60, p=0.93). The findings for $paCO_2$ were similar: values did not substantially differ between good and poor neurological outcomes (42.1 ± 13.6 vs. 46.7 ± 22.9 mmHg; Mann–Whitney U test, p = 0.54), and predictive accuracy was poor (AUC 0.53; 95% CI: 0.43–0.63, p = 0.54).

Initial pH levels, which previously proved accurate to identify patients at risk of death, differed only minimally between survivors with good (CPC 1–2) and poor neurological outcomes (CPC 3–4) (7.30±0.14 vs. 7.30±0.16; Mann–Whitney U test, p=0.61). Consequently, pH demonstrated no meaningful predictive value for poor neurological recovery after cardiac arrest, reflected by an AUC of 0.53 (95% CI: 0.42–0.63, p=0.61). Similarly, serum lactate levels showed only a small difference between groups, with slightly lower concentrations in patients with good neurological outcomes (4.3 vs. 4.8 mmol/L; Mann–Whitney U test, p=0.18). Lactate also demonstrated poor predictive accuracy, with an AUC of 0.57 (95% CI: 0.46–0.68, p=0.18).

Potassium levels also showed only a small difference (4.25±1.06 vs. 4.38±0.90 mmol/L; Mann–Whitney U test, p=0.16), with minimal predictive value (AUC 0.57; 95% CI: 0.46–0.68, p=0.16). Sodium values were likewise similar between outcome groups (137.8±5.1 vs. 138.7±5.4 mmol/L; Mann–Whitney U test, p=0.43), yielding an AUC of 0.54 (95% CI: 0.44–0.64, p=0.43).

Altogether, bicarbonate was the only blood gas parameter to show a significant association to neurological outcomes in hospital survivors of cardiac arrest. However, even for bicarbonate, diagnostic accuracy was very low, rendering it an insignificant prognostic marker at the bedside.

4 Discussion

Cardiac arrest continues to represent a worldwide non-trivial health burden, due to the high number of deaths, substantial costs associated with post-cardiac arrest treatment, and a significant proportion of neurological sequelae. Intra-arrest treatment requires prompt intervention, coordinated teamwork, continuous equipment improvement, and good management in high-intensity situations. Western societies have improved outcomes to some extent by broad people training, from ordinary people who might witness a cardiac arrest to EMS and medical personnel. Post-cardiac arrest care is complex, involving pathophysiological changes associated with ischemic reperfusion syndrome. This phase requires meticulous management, including optimizing oxygenation and ventilation, ensuring adequate perfusion and oxygen delivery, and even considering inducing hypothermia to minimize post-resuscitation neurological dysfunction. Early determination and assessment of the severity of neurological deficiency remain challenging for clinicians managing CA. The clinical practice guidelines now recommend a multimodal assessment to determine neurological outcome post-resuscitation, integrating patient examination, biomarkers, electroencephalography, and imaging. Overall, this multimodal assessment requires time to detect survivors with the potential for neurological recovery.

The prehospital determination of blood gas parameters is becoming increasingly feasible in western healthcare systems, making these markers particularly valuable. After analysing the data from a large dataset of cardiac arrest patients treated at a tertiary German centre, the current work presents several findings:

(1) Among blood gas analysis markers, lactate showed a very strong association with hospital survival (AUROC=0.83), pH (AUROC=0.75), bicarbonate (AUROC=0.73), and base excess (AUROC=0.74) showed good predictive value, and potassium (AUROC=0.73) showed moderate predictive value of hospital survival in cardiac arrest patients.

(2) pH ≤7.2 is associated with a higher mortality risk independently of the cause of acidaemia.

(3) Lactate and pH show only mild collinearity and, when used together, facilitate more granular risk stratification.

(4) In Cox regression analyses adjusted for several CPR characteristics and lactate levels, pH was superior to bicarbonate and base excess in predicting in-hospital mortality.

(5) None of the markers in a standard blood gas analysis are accurate or relevant for predicting neurological outcome.

4.1 Metabolic alterations during and after cardiac arrest

Cardiac arrest and the post-arrest syndrome resemble an extreme form of acute circulatory shock due to similar pathophysiological alterations. In fact, in clinical settings, cardiac arrest and cardiogenic shock frequently coexist. Data from major RCTs indicate that cardiac arrest is frequent in patients with acute myocardial infarction complicated by cardiogenic shock. Moreover, more than half of patients with successful CPR meet clinical criteria for shock, characterized by hypotension requiring vasopressors, rising lactate levels, and the need for intravenous fluid resuscitation [99-101].

These overlapping features highlight the importance of metabolic parameters, particularly pH and lactate, as indicators of systemic derangement in both conditions. This was also mirrored recently by a study, which found a similar finding as the one presented in this work: pH enhances the prognostic accuracy of lactate in cardiogenic shock [74]. While vasopressors remain a mainstay therapy, no other pharmacologic drug has been shown to improve outcomes after cardiac arrest in human studies [102], reinforcing the need for accurate early prognostication based on physiological markers. To standardize risk assessment, the Society for Cardiovascular Angiography and Intervention (SCAI) developed and later updated a classification system for cardiogenic shock. The SCAI shock classification stratifies patients into five categories (A-E) based on clinical, hemodynamic, and biochemical parameters, each associated with distinct mortality rates. The best survival rates were calculated for patients “at risk” of developing cardiogenic shock (SCAI A), with an in-hospital mortality of 1-5%. The worst rates were calculated for patients’ “extremis” (SCAI E), with the highest in-hospital mortality of up to 77% [103, 104]. The entire classification, including all five groups, is shown in Table 10.

CARDIOGENIC SHOCK STAGE		***DEFINITION***
A	At Risk	Hemodynamically stable patient, with neither hypotension or tachycardia, nor hypoperfusion
B	Beginning	Patient with clinical evidence of hemodynamically instability (hypotension, tachycardia but without hypotension)
C	Classic	Patient with clinical evidence of hypoperfusion that requires pharmacological or mechanical support.
D	Deteriorating	Patient with clinical evidence of shock that worsen or fails to improve despite escalation of therapy
E	Extremis	Patient with refractory shock

Table 10: SCAI cardiogenic shock Classification. *Adapted after [103].*

Recently, an analysis of a large cohort showed that patients with cardiac arrest had even higher mortality rates than those with cardiogenic shock alone. Importantly, both the initial heart rhythm and the setting of cardiac arrest (IHCA vs. OHCA) can significantly affect the outcome [101]. Despite shared metabolic patterns, the cause of death following cardiac arrest and cardiogenic shock diverges. In cardiac arrest, anoxic brain injury is the leading cause of mortality after ROS, whereas cardiogenic shock, arrhythmias, multi-organ failure, and refractory hypotension are more predominant. A schematic explaining cerebral changes occurring during and after cardiac arrest is shown in Figure 10.

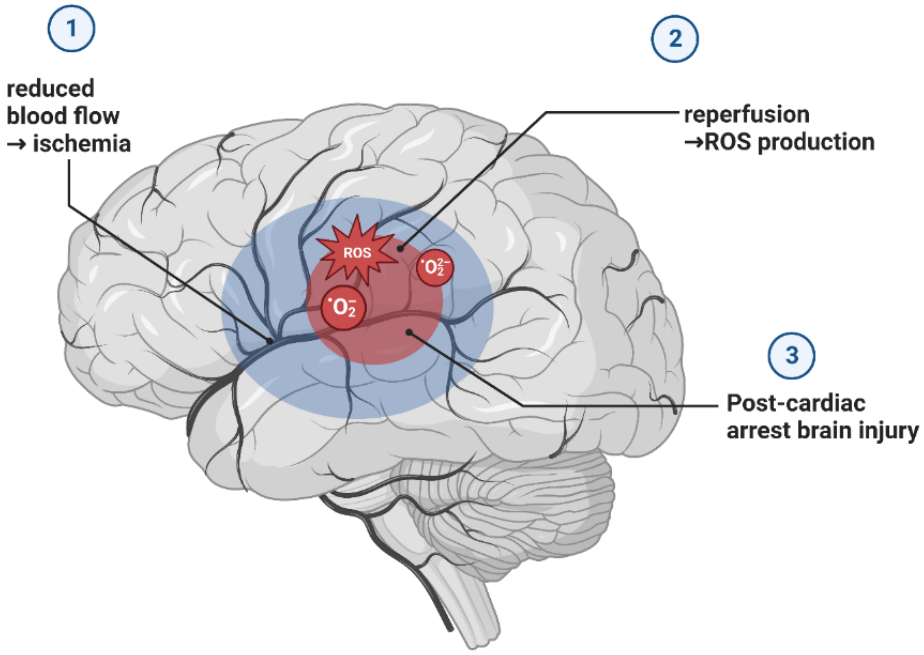

Fig. 10: Cerebral deregulation occurring in the different time-dependent stages after cardiac arrest occurrence. This figure was created in BioRender.

Cardiac arrest triggers a cascade of metabolic disturbances driven by the cessation of circulation and subsequent restoration of perfusion. Two critical phases define this process: the ischemic phase, characterized by inadequate oxygen delivery to cells, and the reperfusion phase, during which the restoration of blood flow causes its own set of injuries. Interestingly, the length of the ischemic phase is definitive for the damage produced in both phases: while this is evident for the ischemic phase (since lack of perfusion leads to oedema, cell swelling, and time-dependent apoptosis), some explanations are needed to understand the reperfusion phase. In the ischemic phase, mitochondrial oxygen tension

drops below the Pascal point (pO_2 0.15-0.3 kPa), triggering a metabolic shift from aerobic to anaerobic energy production. This transition leads to the accumulation of lactic acid, which will dissociate into lactate and hydrogen ions. The resulting acidosis lowers both intra- and extracellular pH, impairing cellular function, disrupting enzymatic activity, and altering the behaviour of ion channels, predominantly leading to hyperkalaemia. Additionally, during reperfusion, hyperoxia induces oxidative stress and generation of reactive oxygen species, causing further damage to mitochondria and cellular metabolism [42], with loss of osmotic control and further ion gradient shift. The current belief is that during a short ischemic phase, there is no damage and no protection during the reperfusion phase (in cellular protection, defined as ischemic conditioning [105, 106].

4.2 Blood gas analysis variables and prognostic biomarkers

Despite ongoing efforts, no single marker has been shown to reliably predict the ROSC after cardiac arrest. Therefore, clinicians rely on a combination of clinical and paraclinical tools to identify patients with the potential for ROSC. The above-described pathophysiological changes underpin the clinical relevance and perhaps some diagnostic potential of blood gas analysis in cardiac arrest. Assessments of these parameters enable clinicians to rule out some of the reversible causes of cardiac arrest, allowing for more targeted interventions and improving the chances of successful resuscitation. In fact, multiple studies have evaluated blood gas analysis parameters as prognostic tools in critically ill patients. Among the various parameters analysed, lactate and pH emerged as significant, supported by multiple studies that highlight their critical role in prognosing severe, life-threatening conditions [66, 68].

Acidosis, defined as a pH <7.35, can be either respiratory, characterized by a CO_2 level exceeding 45 mmHg, or metabolic, due to an increase in hydrogen ion concentration and a decrease in the bicarbonate concentration. Metabolic acidosis can be further classified into two categories based on anion gap: normal-gap and high-gap. The anion gap is a calculated value that represents the difference between cations and anions in the blood and serves as an estimate of the presence of unmeasured anions, which can cause metabolic acidaemia. This acid-base disorder is commonly observed in intensive care patients, including those suffering from cardiogenic shock, respiratory insufficiency, sepsis, and trauma, all of which significantly affect prognosis and disease progression [107, 108]. Numerous studies have established that metabolic acidosis is associated with increased mortality rates among critically ill patients [109]. Regarding the prognostic significance of pH in OHCA or IHCA, multiple studies have shown that low pH is associated with a poor prognosis in patients resuscitated from OHCA. Consequently, patients who achieve early metabolic resolution

experience a reduced incidence of multiple organ dysfunction and lower early mortality rates.

Lactate is a negatively charged ion that forms when the body breaks down carbohydrates under low oxygen conditions. It is predominantly produced in muscle, red cells, brain, skin, and gastrointestinal cells in conditions of high metabolic demand. Lactate is transported via the bloodstream to the liver, where it is converted back into glucose via gluconeogenesis, a pathway known as the Cori cycle. A small part can be used from heart cells and kidneys as an energy source. Hyperlactatemia reflects tissue hypoperfusion and inadequate oxygen delivery. This can lead to acidaemia, which further contributes to hemodynamic instability, vasodilatation, and reduced response to endogenous and exogenous catecholamines. Moreover, elevated lactate levels indicate a shift toward anaerobic metabolism and are known to impair left ventricular contractility and decrease catecholamine responsiveness. Severe acidosis can trigger the production of proinflammatory mediators such as tumor necrosis factor-alfa and nitric oxide, which can contribute to complications both during cardiac arrest and in the post-ROSC period. Although no defined cut-off values for pH and lactate have been established in the literature, the trend in lactate clearance appears more predictive than the initial value alone.

Early identification of patients with a favourable outcome can be supported by analysing additional metabolic parameters, such as pH, lactate, and BE, and by combining their interpretations to understand the underlying metabolic disturbance better. Evidence for this approach comes from a prospectively collected 14-year database from Vienna [110], which included a majority of the OHCA population. Because the causes of cardiac arrest differ between IHCA and OHCA, with respiratory aetiologies more common in IHCA, the authors found that a detailed metabolic assessment may help predict IHCA outcomes. In contrast, within the OHCA cohort, these metabolic parameters did not demonstrate significant predictive value [110]. Consequently, current guidelines recommend measuring lactate levels after ROSC to assess perfusion adequacy, and several studies confirm that survivors tend to have lower initial lactate levels and faster lactate clearance [71].

Pathophysiologically, pH denotes the concentration of protons in a medium. Since protons react with bicarbonate by transforming into water and carbon dioxide as a ubiquitous reaction in the human body, an inverse relationship between pH and bicarbonate was expected. Bicarbonate serves as a primary extracellular buffer and plays a crucial role in maintaining acid-base homeostasis. Its concentration reflects the metabolic component of acid-base balance and can provide indirect insight into the severity of metabolic acidosis. Despite this, its prognostic utility may be limited by its dependency on both respiratory and renal compensatory mechanisms, which can obscure direct interpretation in critically ill patients. Similarly, base excess represents the amount of strong acid or base that must be

added to return blood pH to normal under standardized conditions. It thus provides a more standardized and comprehensive estimate of the metabolic component of acid-base disturbance. A markedly negative base excess typically reflects severe metabolic acidosis and has been associated with poor clinical outcomes [111]. To fully understand which one is primary, the base excess and the bicarbonate are indicators of metabolic acid-base balance independent of the respiratory component. Base excess plays a role in risk stratification of OHCA survivors; lower BE (<8.5) has significantly lower survival and neurological good outcomes after ICU discharge than BE of <2 [112]. These findings highlight the need to include metabolic markers in a comprehensive early evaluation.

In addition to pH and lactate, paO_2 and $paCO_2$ provide valuable information on oxygenation and ventilation status and showed moderate accuracy in predicting in-hospital mortality. In addition, hypoxia, hypercapnia, and hypocapnia are recognized as reversible causes of cardiac arrest. Therefore, it is mandatory to have information regarding ventilation and oxygenation during resuscitation. Hypoxemia represents low oxygen levels in the blood (low paO_2) and will lead to mitochondrial damage, dysfunction in cell metabolism, and acidosis, all of which contribute to tissue damage. Hypoxia represents a risk factor in the appearance of hypoxic brain injury, whose pathophysiology was explained in a previous chapter. Briefly, following a period of no-flow time, reintroducing oxygen to the tissue might have both beneficial and detrimental effects. Reoxygenation triggers a systemic inflammatory response by producing inflammatory mediators, which can lead to endothelial dysfunction and capillary leakage. Hyperoxia might induce oxidative stress, with a large amount of reactive oxygen species causing damage to the cellular components such as DNA and proteins, and contributing to apoptosis.

Among the most informative real-life indicators during CPR is end-tidal CO_2 ($etCO_2$), which reflects both the quality of CPR and pulmonary blood flow. Persistently low $etCO_2$ values during resuscitation are associated with a poor prognosis, while a sudden and sustained increase often indicates ROSC [113]. In fact, CO_2 plays a crucial role during cardiac arrest. Hypercapnia or high levels of CO_2 can lead to respiratory acidosis, impairing myocardial function, promoting arrhythmia, or inefficiency of resuscitation drugs. Post-ROSC it remains a surrogate for cerebral circulation due to its regulatory effects on cerebral blood flow. Hypocapnia induces cerebral vasoconstriction, which can worsen ischemic injury, while hypercapnia increases cerebral blood flow. Therefore, current guidelines recommend maintaining normocapnia after ROSC [7, 114]. Notably, multiple studies have reported worse outcomes associated with hypocapnia compared to hypercapnia [115].

Cardiac arrest is frequently associated with electrolyte imbalances, particularly affecting potassium, although abnormalities in calcium and magnesium levels can also be involved. Potassium is a critical intracellular electrolyte whose concentration is strictly regulated

because both hypo- and hyperkalaemia can trigger life-threatening arrhythmias and cardiac arrest. Furthermore, acidosis can exacerbate hyperkalaemia by impairing the normal exchange of hydrogen and potassium ions across the cell membrane, leading to a shift of potassium from the intracellular to the extracellular space. Serum potassium levels of 8mEq/L are considered critically high and may be fatal if not promptly corrected. Interestingly, some studies have suggested that cardiac arrest survivors with a pH > 6.8 and a potassium level < 8.5 mEq/L may still achieve a good neurological outcome [116]. Calcium and magnesium are essential for myocardial contractility and electrical stability, and an imbalance between them during cardiac arrest might impair heart function. Additionally, sodium disturbance has been linked to post-cardiac neurological outcomes, due to its effect on cerebral oedema, osmotic balance, and neurological excitability. In comatose survival of a cardiac arrest, hyponatremia was the most common and associated with a lower probability of a favourable outcome [117]. Overall, careful monitoring and timely correction of oxygenation, ventilation, and electrolyte imbalances are crucial not only for the acute management of cardiac arrest but also for optimizing post-resuscitation care and improving long-term neurological recovery.

In line with previous studies, the current analyses showed that low pH and elevated lactate levels following cardiac arrest were strongly associated with increased mortality. While lactate remains a crucial indicator of tissue hypoperfusion, the current analyses showed that pH not only independently predicts survival, with a clear threshold at ≤ 7.2, but also enhances the predictive power of lactate when combined. In contrast, bicarbonate and base excess had some predicted value, inferior to that of pH. This overlap with the existing literature further highlights the robustness of pH as a key marker in early risk stratification for cardiac arrest outcomes.

4.3 Blood gas analysis and neurological outcomes

Cessation of blood flow in cardiac arrest leads within 10-30 seconds to the onset of a coma due to absent cerebral circulation. Neurons are highly susceptible to ischemia, and if blood flow remains interrupted, apoptosis is inevitable within the first hour. This process, known as hypoxic-ischemic encephalopathy, remains the leading cause of death or long-term disability in patients who have been successfully resuscitated after cardiac arrest. A second damaging mechanism occurs during reperfusion, when restored blood flow paradoxically leads to further neuronal injury through oxidative stress and inflammation [8].

Among the key factors for exacerbating post-cardiac arrest brain injury, hypoperfusion plays a crucial role. CO_2 and pCO_2 are key regulators of cerebral blood flow. Data from previous studies concluded that hypocapnia can worsen brain injuries, leading to an

association with poor neurological outcomes [115]. In contrast, mild hypercapnia has been linked to improved 12-month survival rates in cardiac arrest survivors [118]. Very recently, the TAME study examined whether mild hypercapnia (50-55 mmHg) was indeed associated with better long-term neurological outcome than normocapnia (35-45 mmHg) in cardiac arrest patients after CPR in a randomized-controlled trial across 17 countries. The authors found no added benefit of mild hypercapnia over normocapnia after OHCA [56].

Oxygen administration is a trivial part of CPR therapy, and often, it is carried out even after ROSC. Retrospective data show that as many as 40% of post-CPR patients are exposed to high oxygen concentrations [119]. However, whether exposure to such high concentrations is beneficial for the patients remains open to question. On the one hand, hyperoxia after ROSC can worsen brain damage, most probably due to higher ROS synthesis. On the other hand, it is unclear whether differences in oxygenation directly affect outcomes.

Observational trials examining the association between oxygenation and outcomes are highly heterogeneous. A recent systematic review and meta-analysis by the International Liaison Committee on Resuscitation highlighted the variability and issued a mild recommendation in favour of normoxia [120]. Notably, a large prospective multicentre trial demonstrated that exposure to high oxygen concentrations after resuscitation was associated with worse neurological function at hospital discharge [121]. In line, in a post hoc analysis of the Target Temperature Management (TTM) trial, neither hypoxia nor hyperoxia was associated with any changes in neurological outcome within the first three days after ROSC [122].

The effect of targeted oxygen administration was also investigated in phase 2 trials; however, these primarily used O_2 saturation rather than the direct partial pressure as the primary endpoint. One RCT investigated the link between O_2 and neurological outcome (measured by NSE and S-100). The investigators found that administering 30% O_2 was as safe as administering 100%. Moreover, 100% O_2 administration led to higher NSE levels [123]. The small number of patients included (n=28) should be considered when interpreting the results.

While the data presented in this work did not specifically address the association between different oxygen levels and outcomes after cardiac arrest, the analysis of initial pO_2 levels did not reveal any link to later neurological outcomes. One possible explanation could be linked to blood withdrawal shortly after arrival at the centre, where extrinsic O_2 administration might be very high.

Considered a predictive marker of hemodynamic status, serum lactate is a quick and easy parameter for assessing circulatory failure and a prognostic marker of cardiac arrest. Multiple studies have investigated the use of lactate as a predictor of good neurological

recovery. Among these, the CRITICAL study [76] was a multicentre, prospective study conducted in Japan that examined 30-day survival and good neurological outcomes in OHCA patients. They concluded that high lactate levels during CPR were associated with lower 1-month survival, regardless of the initial rhythm or lactate level. However, the number of patients with favourable neurological recovery in this cohort was relatively small, limiting the strength of the conclusion.

Serial lactate measurements within the first 48 hours after cardiac arrest may help stratify survivors and non-survivors based on their initial lactate level. Early and adequate lactate clearance is associated with decreased mortality, while persistent hyperlactatemia appears to be a marker of poor prognosis [53]. One study states that a poor prognosis is particularly evident when high lactate levels at admission are accompanied by slow metabolism within the first 24 hours post-cardiac arrest. In contrast, survivors with favourable neurological outcomes (CPC I-II) tend to have lower lactate levels at admission [97]. A multicentre prospective study from 2014 reinforced the theory that better neurological outcomes were associated with lower initial lactate levels and more efficient lactate clearance within the first 12-24 hours post-cardiac arrest [124].

Despite the growing literature on the subject, no universally accepted cut-off value for serum lactate has been established to reliably predict neurological outcome. Instead, greater emphasis is placed on lactate clearance as a more valuable indicator. The current analysis demonstrated that a lower admission serum lactate level was associated with better survival, and among hospital survivors, those with a good neurological outcome had slightly lower lactate levels (4.3 vs. 4.8 mmol/L). However, the difference was not significant. A potential explanation for these findings may lie in the heterogeneity of physiological responses to therapeutic interventions and the presence of associated comorbidities within the current study population, which could have influenced lactate metabolism and prognostic utility, and in the low number of hospital survivors in the analysis (n=196).

Metabolic imbalance, particularly acidosis, is a frequent consequence in survivors of cardiac arrest, which can disrupt cellular function. This imbalance has been linked to both reduced survival and poor neurological outcomes. Following an OHCA, pH abnormalities, especially acidosis, are seen frequently after ROSC. Notably, pH value serves as a crucial predictor of outcomes, with higher pH values being associated with improved neurological recovery and better outcomes [125]. For instance, the retrospective cohort study, the ROC ALPS trial, reported an initial median pH of 7.21, with values rising progressively in both the survivor and non-survivor groups during the first 6 hours post-ROSC before stabilizing. Although many studies support the association between higher pH and better outcomes in OHCA patients, no universally accepted threshold has been established. A Japanese study proposed a pH cut-off >7.05 for predicting good neurological outcome [98]. However, the

retrospective design and the relatively small sample size limits its generalizability to the broader population. A recent retrospective analysis of the JAAM-OHCA [126] register demonstrated that even patients with severe acidosis might achieve good neurological recovery if certain demographic factors are present, such as a witness cardiac arrest and an initial rhythm like PEA or VT.

Beyond pH, base excess offers an additional lens through which to evaluate metabolic derangement after ROSC. As an indicator of acidosis severity, BE can aid early risk stratification. While extreme BE values, both low and high, have been associated with increased mortality in heart failure, data regarding their prognostic significance in cardiac arrest remain limited. Severe metabolic acidosis is associated with refractory shock states and is characterized by elevated lactate levels and accumulation of unmeasured anions; therefore, patients with lower BE values (0 to 9) may have better neurological outcomes, quantified as CPC I–II [127]. Moreover, existing studies predominantly report outcomes in patients receiving extracorporeal support, underscoring the need for further investigation in broader cohorts.

Among electrolyte disturbances observed after cardiac arrest, potassium imbalance is the most common. Both hypokalaemia and hyperkalaemia can impact normal cellular function, but hyperkalaemia appears to have a more detrimental impact on outcome. In OHCA survivors, higher potassium levels at admission tended to have an unfavourable functional outcome, whereas hypokalaemia did not appear to play as significant a role [128]. The Comprehensive Registry of Intensive Cares for OHCA Survival (the CRITICAL) trial, a prospective study across 14 ICUs in Osaka, Japan, which included over 1500 OHCA patients, found a dose-dependent relationship between rising potassium levels and worse neurological outcomes [129].

In the current analysis, serum potassium levels showed a small difference between patients with good and poor outcomes, but this variation did not reach statistical significance in prognostic prediction. Similarly, base excess values were similar between the two groups, suggesting that this parameter does not serve as a reliable independent predictor of neurological recovery in the current data.

4.4 Risk stratification scores

Various scoring systems have been developed to predict outcomes by integrating multiple clinical and physiological factors, aiding in guiding clinical interventions and resource management. Depending on the stage of care, different scoring systems can be applied to predict ROSC, hospital discharge survival, or neurological outcomes.

A known scoring system specifically designed to predict a ROSC is the Risk Analysis for Cardiac Arrest (RACA) score [130]. Initially developed on 5471 prospectively OHCA patients included in the German Resuscitation Registry between 1998 and 2008, the score considered age, cardiac arrest aetiology, initial rhythm, location, whether the event was witnessed, and whether bystander CPR was performed, and showed moderate to good prognostic accuracy in the initial and later validation cohorts [130-132]. However, a key limitation of the RACA score is the large number of variables included, which makes it difficult to calculate and apply in the high-intensity setting of cardiac arrest.

Several other scoring systems have been developed to predict survival at hospital discharge following cardiac arrest. Among the most frequently referenced scores are PCAC (Pittsburgh Cardiac Arrest Category), and CREST scores. The PCAC score assesses the severity of early post-resuscitation illness and serves as a valuable tool in predicting in-hospital mortality, multiorgan failure, and favourable outcomes at hospital discharge [133]. It is applicable in both IHCA and OHCA cases and is recognized for its simplicity in clinical application. By contrast, the CREST score is more narrowly focused, having been designed explicitly for cardiac arrest survivors without ST-segment-elevation myocardial infarction [134]. A recent retrospective study [135] conducted in the UK sought to validate the CREST score for risk stratification of circulatory aetiology death in patients presenting with OHCA without evidence of STEMI. The study concluded that while the CREST score may be useful in this context, incorporating additional parameters, such as lactate levels and arterial pH, could enhance its predictive accuracy. However, it is essential to note that this is currently the only study currently available in the literature utilizing the CREST score for predicting circulatory aetiology death, which imposes certain limitations on its generalizability and broader applicability.

The CAHP (Cardiac Arrest Hospital Prognostic) score was developed to identify patients at elevated risk of poor neurological outcomes who may derive limited benefit from immediate cardiac catheterization or advanced hemodynamic devices [136]. This prognostic tool was designed for adult patients with ROSC presenting to the emergency department. The CAHP score incorporates several clinician variables, including patient age, initial cardiac rhythm, location of cardiac arrest, time from collapse to CPR initiation, time from CPR initiation to ROSC, cumulative doses of administered epinephrine, and arterial pH at admission. Based on this parameter, patients are stratified into low, moderate, and high-risk categories for poor neurological outcomes, corresponding to a CPC of III–V, with associated rates of 29.6%, 86.3%, and 99%, respectively. However, its clinical applicability may be constrained by the challenges associated with accurately estimating no-flow time, particularly in contemporary practice, where simpler scoring systems are increasingly available. A recent retrospective study [137] comparing the CAHP score with the MIRACLE2

score in predicting neurological outcomes following OHCA demonstrated that, while the CAHP score exhibits superior discriminative capacity, it may be more complex and less practical to implement in routine clinical settings.

The MIRACLE2 score is a relatively recent addition to prognostic tools designed to predict early neurological outcomes in OHCA patients [138]. It was developed to redefine survival predictions and enhance early risk stratification. The score comprises seven variables, yielding a maximum of 10 points, and classifies patients into three risk categories: low risk (MIRACLE2 score 1-2), intermediate risk (MIRACLE2 score 3-4), and high risk (MIRACLE2 score >5). The variables used to calculate the MIRACLE 2 score are largely similar to those used in the CAHP score, although a key distinguishing factor is the emphasis on neurological assessment, particularly the documentation of pupil reactivity after ROSC. The authors highlighted the MIRACLE2 score as a straightforward and practical tool for predicting poor neurological outcomes at the point of admission in ED, thereby aiding clinicians in making rapid, informed decisions [138]. In comparative analysis, the MIRACLE2 score has been evaluated against other established scoring systems, including the CAHP, TTM and OHCA score. These analyses have demonstrated that the MIRACLE2 score offers superior or comparable discriminatory ability, with the added advantages of ease of calculation and practical applicability in clinical settings. Furthermore, a separate retrospective study sought to validate the MIRACLE 2 score as a simple risk stratification tool in predicting poor neurological outcomes in patients with OHCA of presumed cardiac origin[139]. The study concluded that patients categorized as intermediate risk (MIRACLE 2) represent the most uncertain group in terms of prognostication. This reflects an inherent limitation of all scoring systems and underscores the importance of clinical judgment, particularly for this vulnerable subgroup, where nuanced decision-making may ultimately influence patients' outcomes.

Two major trials have recently investigated the effects of temperature on survival and neurological outcome. The Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial assigned 950 OHCA patients with presumed cardiac cause to either 33°C or 36°C. The authors found similar mortality and proportion of poor neurologic function at the endpoint 180 days [140]. In the second Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial, 1850 patients were assigned to either targeted hypothermia (33°C), followed by controlled rewarming, or targeted normothermia with fever prevention. Similar to the TTM-trial, the authors found no benefit in terms of mortality or neurological outcome from hypothermia [141]. Based on the cohort of Targeted Temperature Management, a further score was developed in 2017, unofficially named Target Temperature Management (TTM) score, which incorporated ten variables that are readily available upon the patient's admission to the

emergency department [142]. Its parameter aligned with those used in previously described scoring models; however, it differed by incorporating additional assessment of pCO_2 and Glasgow Coma Score (GCS). The TTM scores range from -2 to 35, with higher value indicating a poorer prognosis. Kägi et al. [143] attempted to validate the TTM score in a small cohort of 100 patients in Bern, Switzerland. Their study concluded that a cut-off of 16 points could effectively identify patients with poor neurological outcomes following cardiac arrest, while also highlighting a vulnerable subgroup with scores between 11 and 16 points. Additionally, the study addressed the limitation of using the GCS motor response in intubated and sedated patients, where its applicability is restricted.

Recently, the performance of the four prognostic risk scores, TTM, MIRACLE2, OHCA, and CAHP, was assessed for their ability to predict a combined endpoint of poor functional outcome (modified Rankin Scale scores of 4–6) or death at six months post-OHCA in a post-hoc analysis of the TTM2-trial [144]. The findings showed very high prognostic accuracy for all four scores: CAHP-score: AUROC: 0.82 (95% CI: 0.80–0.84); MIRACLE2-score: 0.81 (95% CI: 0.79–0.83); OHCA-score: 0.77 (95% CI: 0.74–0.79); TTM-score: 0.84 (95% CI: 0.81–0.85). Given the simplicity of the MIRACLE2 score, the authors concluded that in light of a similar prognostic accuracy, this score was particularly practical for routine clinical application and risk stratification in clinical trials [144].

Specially designed for patients who experience IHCA, the Good Outcome Following Attempted Resuscitation (GO-FAR) score predicts the likelihood of survival to hospital discharge, with particular emphasis on good neurological outcomes [145]. This scoring system is derived from the evaluation of 13 prearrest variables, including age, neurological status, cardiovascular condition, renal, and pulmonary function. The GO-FAR score stratifies patients into four distinct groups based on their predicted outcome. A GO-FAR score ranging from -15 to -6 points indicates a higher-than-average likelihood of survival, while a score between -5 and 13 points denotes an average survival prognosis. Patients with scores between 14 and 23 are considered to have a low chance of survival, and scores exceeding 24 indicate a very low probability of survival. The GO-FAR score is specifically designed to assess the likelihood of a good neurological outcome (CPC I) in hospitalized patients upon discharge after IHCA. The validity of the GO-FAR score in predicting a favourable neurological outcome after IHCA was established by Ebell et al., who conducted a study utilizing data from 366 hospitals in the Get with the Guidelines Resuscitation registry [146, 147]. Their findings demonstrated that the GO-FAR score successfully identified 9.4% of patients with a very low likelihood of a favourable neurological outcome after IHCA and 18.9% with a low probability of a good neurological outcome after IHCA [146, 147]. This study supports the clinical utility of the GO-FAR score, providing healthcare providers with

a helpful tool to guide decisions regarding the continuation or cessation of life-sustaining therapy.

Altogether, while these risk stratification scores provide an objective framework for assessing post-cardiac arrest outcomes and show mostly high diagnostic accuracy, several of these risk scores incorporate lactate and pH levels as individual variables in their calculations. This emphasizes the importance of these markers for mortality and neurologic prognostication, along with the established clinical algorithms in most hospitals, for assessing these parameters during and after CPR and for relying further on algorithms based on their absolute values.

5 Conclusion

In this cohort of non-traumatic cardiac arrest patients, analysis of arterial blood gas parameters obtained at hospital admission showed that several biomarkers retain prognostic information on 30-day mortality. Serum lactate, a marker of perfusion, remains the most precise biomarker for in-hospital mortality prediction and is feasible for routine clinical use. pCO_2 helps quantify tissue hypoxia as a marker of hypoventilation. The arterial pH integrates both metabolic and respiratory disturbances and, in line, yielded prognostic accuracy. Especially $pH \leq 7.2$ should be considered as a marker of high mortality risk in cardiac arrest patients. Combining pH and lactate levels enables more granular risk stratification of cardiac arrest patients, demonstrating pH value beyond lactate alone. The increasing availability of prehospital blood gas analysis will allow earlier determination of these biomarkers, leading to better discrimination of patients with worse outcomes, thereby improving resource allocation and healthcare systems' costs. Lactate and pH are among the variables in several scoring systems (MIRACLE 2, CAHP, and TTM) proposed for predicting mortality and neurological outcomes, and these systems demonstrated accurate discrimination in external studies. The current work reinforces the rationale for their inclusion by demonstrating the clinical value of these biomarkers.

In this analysis, none of the blood gas parameters was associated with neurological outcomes among hospital survivors. This finding contrasts with previous literature, which has reported predictive value for lactate and pH. However, unlike most prior studies, the current analysis accounted for mortality bias by excluding deceased patients, thereby addressing the high mortality rates inherent to OHCA and IHCA cohorts. Altogether, pH primarily reflects global metabolic stress, rather than cerebral injury.

In light of the present findings, the following recommendations and future directions are proposed: The association between acidemia, severe acidemia, and in-hospital mortality should be confirmed in larger prospective cohorts. Given the readily available resources, a pH threshold of ≤7.2 may be used clinically to identify patients at higher risk of in-hospital mortality and should complement other established prognostic markers. Prospective studies in adequately powered cohorts of cardiac arrest survivors are needed to confirm whether blood gas analysis variables have any predictive value for neurological outcomes.

6 Strengths and limitations

This study offers several methodological and clinical strengths that enhance the validity and applicability of its findings. First, the study cohort originates from the University Clinic of Düsseldorf, a major German tertiary care center providing high-quality medical management and advanced mechanical support in accordance with contemporary guidelines. The large number of cardiac arrest patients treated at this center enabled robust statistical analyses, and the high degree of data completeness permitted meaningful subgroup evaluations and appropriate adjustment. Second, the arterial origin of the blood gas samples ensured accurate assessment of metabolic and respiratory status. Third, nearly all patients had a documented neurological outcome at hospital discharge, allowing reliable evaluation of neuroprognostic performance. Fourth, the comprehensive adjustment for multiple biomarkers reflecting systemic perfusion, ventilatory status, and acid–base balance, particularly serum lactate and pCO_2, strengthened the evidence for arterial pH as an independent prognostic marker. Finally, the restriction of neurological outcome analysis to survivors represents a methodological advantage over previous studies that were biased by the high proportion of non-survivors.

Despite these strengths, several limitations must be acknowledged. The retrospective nature of the study design precludes causal inference. Second, the relatively small number of survivors in the analysis might have limited the power to detect a possible association between arterial blood gas analysis parameters and neurological outcome. In addition, the current analysis on neurological outcome was only performed in hospital survivors. Third, the observation period is slightly older, making validation of the data in contemporary cohorts necessary. Fourth, the data presented were derived only from a single-centre clinical population. Although the study included both OHCA and IHCA, the predominance of the IHCA population may limit the generalizability of the findings to other populations.

7 References

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