Galectin-3 as a marker to characterize post-cardiac arrest syndrome in initially survived out-of-hospital cardiac arrest: a prospective two-center study

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Content

Summary

Background: Survivors after out-of-hospital cardiac arrest (OHCA) subsequently experience post-cardiac arrest syndrome (PCAS), which encompasses hemodynamic instability, systemic inflammation and brain injury and contributes to high in-hospital mortality rates. The present study aims to elucidate the relationship between serial galectin-3 (GAL3) levels and survival, neurological outcome, cardiovascular failure and inflammation after OHCA.

Methods: This prospective, two-center study included 71 adults after non-traumatic OHCA. Blood samples were taken on hospital admission (day 0) and day 2 after return of spontaneous circulation (ROSC). Serum GAL3 concentrations were quantified by enzyme-linked immunosorbent assay and compared to serum levels of 39 patients with coronary artery disease (CAD).

Results: Serum GAL3 levels were highest on day 0 and declined on day 2 after ROSC to levels comparable to CAD controls. In a logistic regression model, GAL3 levels >37.48 ng/ml were a significant predictor for in-hospital mortality. GAL3 on day 0 was not associated with neurological outcome assessed by Cerebral Performance Category or neuron-specific enolase but was higher in patients with brain edema on cerebral computed tomography. No association was observed between GAL3 and cardiac causes of OHCA, NT-proBNP levels or myocardial dysfunction. Notably, GAL3 levels on admission were significantly higher in patients with inadequate lactate clearance and GAL3 levels on day 2 were elevated in OHCA patients who required prolonged vasopressor/inotropic application, both indicators of persistent hypoperfusion and shock. In addition, a positive correlation of GAL3 on day 0 and levels of interleukin-6 on day 0, a marker of PCAS severity, was observed.

Conclusion: Serum GAL3 levels are associated with in-hospital mortality and distinct features of PCAS including cerebral edema, persistent shock and systemic inflammation following OHCA.

Zusammenfassung

Hintergrund: Patient:innen nach außerklinischem Herz-Kreislauf-Stillstand (out-of-hospital cardiac arrest, OHCA) entwickeln in der Folge ein Post-Herz-Kreislauf-Stillstands-Syndrom (post-cardiac arrest syndrome, PCAS). Dieses umfasst hämodynamische Instabilität, systemische Entzündungsprozesse und hypoxische Hirnschädigung und trägt zu hohen innerklinischen Sterblichkeitsraten bei. Die vorliegende Studie untersucht den Zusammenhang zwischen seriellen Galectin-3 (GAL3) Spiegeln und dem Überleben, dem neurologischen Outcome, der hämodynamischen Situation und Inflammationsprozessen nach OHCA.

Methoden: In dieser prospektiven, bizentrischen Studie wurden 71 Erwachsene nach einem nicht-traumatischen OHCA eingeschlossen. Blutproben wurden bei Krankenhausaufnahme (Tag 0) und an Tag 2 nach Wiederherstellung des Spontankreislaufs (return of spontaneous circulation, ROSC) entnommen. Die Serum-GAL3-Konzentrationen wurden mittels enzyme-linked immunosorbent assay quantifiziert und mit den Serumspiegeln von 39 Patient:innen mit koronarer Herzkrankheit (KHK) verglichen.

Ergebnisse: Serum-GAL3-Spiegel waren an Tag 0 am höchsten und sanken an Tag 2 nach ROSC auf Werte, die mit denen der KHK-Kontrollgruppe vergleichbar waren. In einem logistischen Regressionsmodell waren GAL3-Spiegel >37,48 ng/ml ein signifikanter Prädiktor für die innerklinische Mortalität. GAL3 an Tag 0 war nicht mit der Neuronenspezifischen Enolase oder dem neurologischen Outcome gemäß Cerebral Performance Category assoziiert. Es war jedoch bei Patient:innen mit Hirnödem im zerebralen Computertomogramm signifikant erhöht. Es wurde keine Assoziation zwischen GAL3 und kardialen Ursachen des OHCA, NT-proBNP-Spiegeln oder myokardialer Dysfunktion beobachtet. Allerdings waren die GAL3-Spiegel bei Aufnahme signifikant höher bei Patient:innen mit persistierend erhöhtem Laktat. Als weiterer Indikator für anhaltende Hypoperfusion und Schock waren die GAL3-Spiegel an Tag 2 erhöht bei OHCA-Patient:innen, welche eine längere Vasopressor-/Inotropika-Anwendung benötigten. Zusätzlich wurde eine positive Korrelation von Interleukin-6 – einem Marker für den Grad der PCAS-Ausprägung – und GAL3 bei Aufnahme beobachtet.

Schlussfolgerung: Serum-GAL3-Spiegel sind mit innerklinischer Mortalität und spezifischen Merkmalen des PCAS wie Hirnödem, anhaltendem Schock und systemischer Inflammation nach außerklinischem Herz-Kreislauf-Stillstand assoziiert.

Background

Epidemiology and etiology of out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the Western world and patients who initially survive OHCA face a poor prognosis [1, 2]. In 2024, the German resuscitation registry (Deutsches Reanimationsregister) reported an overall incidence of 124.9 per 100.000 population [3]. An average annual incidence of 82 per 100.000 population is recognized in the current European resuscitation council (ERC) guidelines [2]. OHCA incidence has remained stable in the last years [2].

About 2/3 of German resuscitated patients in 2024 were male (65.3%) and the average age was 69.4 years [3]. Witnessed arrests occurred in 56.9% of all cardiac arrests (CA) and laymen cardiopulmonary resuscitation (CPR) commenced in 60.2% of cases [3]. This is in line with the European average of 58% bystander CPR [2, 4]. As in other European countries, asystole was the predominant first rhythm in Germany in 2024 (56.3%). Shockable first rhythm was registered in 22.5% of all cases [3, 4].

For 2024, the majority of German cases (52.3%) were of assumed cardiac etiology [3]. Acute coronary syndrome causes about half of all OHCA and troponin-T elevation on admission has been observed in 40% of patients [5, 6]. Respiratory causes were suggested for 14.2% of cases [3].

Pathophysiology of ischemia/reperfusion injury

Cardiac arrest with successful resuscitation and return of spontaneous circulation (ROSC) leads to whole-body ischemia/reperfusion (I/R) injury [7]. This complex phenomenon encompasses damaging processes both during the initial ischemic as well as the subsequent reperfusion phase and involves a sterile inflammatory response [7, 8].

The ischemic phase is characterized by an insufficient supply of oxygen and metabolic substrates [7]. Adenosine triphosphate (ATP) depletion leads to cell necrosis and activation of autophagic and apoptotic processes ensues [7]. Even after ROSC, ongoing myocardial dysfunction and hemodynamic instability can cause sustained oxygen deficiency [1].

The reintroduction of oxygen during the reperfusion phase is paradoxically damaging. It leads to excessive production of reactive oxygen species (ROS) that disintegrate proteins, lipids and deoxyribonucleic acid (DNA) and cause mitochondrial injury [7, 8]. Reperfusion also leads to a massive influx of inflammatory stimuli [7, 9-12].

The sterile inflammatory reaction of I/R injury includes both the innate and the acquired immune system. The innate immune response is triggered by damage associated molecular patterns that get expressed extracellularly due to oxidative stress and following necrotic cell death. After binding to their ligands (e.g. toll-like receptors),

cytokine production including tumor necrosis factor (TNF)α, interleukin (IL)-1, IL-6, IL-8, and IL-10 is induced [10]. Moreover, cytokines and chemokines lead to recruitment of granulocytes, monocytes and dendritic cells during the early reperfusion phase [7, 8]. Activation of the complement system further maintains these processes of cytokine production and immune cell infiltration [7, 8].

The response of the acquired immune system includes T-lymphocyte recruitment to and accumulation in damaged tissue [7]. T-lymphocytes in turn produce interleukins that can exert both pro-inflammatory and protective features [7].

Microvascular dysfunction is another hallmark pathophysiological feature of I/R. The disbalance between oxygen supply and demand causes a so called “oxygen debt” and triggers adaptive endothelial mechanisms [1]. The endothelial activation is based on an intracellular deficiency of oxygen-dependent second messenger proteins [13]. This results in compromised regulation of vasoconstriction and -dilation with excessive production of vasoconstrictive substances such as endothelin-1, increased vascular permeability and activation of thrombocytes as well as complement cascades [7, 13]. Microvascular dysfunction inhibits vascular relaxation during reperfusion, causes the no-reflow phenomenon, and thus, impedes perfusion even after ROSC [7].

Post-cardiac arrest syndrome

After achieving ROSC, whole body I/R injury causes post-cardiac arrest syndrome (PCAS). PCAS consists of myocardial dysfunction with hemodynamic instability, hypoxic-ischemic encephalopathy (HIE) and a systemic inflammatory syndrome that leads to multi-organ failure [1, 14]. Furthermore, a persisting precipitating pathology might further destabilize patients [1].

Depending on the duration of ischemia, four broad phases can be distinguished. Microvascular dysfunction predominates in the first 24 hours (h) and induces the release of free radicals in the patients’ blood [1, 11]. This includes hydroxyl and superoxide radicals which cause myocardial cell dysfunction and promote a global but reversible limitation of myocardial function commonly referred to as post-cardiac arrest myocardial dysfunction (PCAMD) [12, 15, 16]. Clinically, PCAMD is defined as a state of reduced left-ventricular ejection fraction (LVEF) and impaired vasoregulation causing hemodynamic instability with need for vasopressor support. PCAMD is reversible, lasts between 4-72 h after resuscitation from CA and is a major contributor to poor outcome [14, 17-19]. The prevalence of PCAMD after OHCA varies between 34-75% [18, 20, 21]. It can be caused by left or right ventricular dysfunction and affects both parts of the cardiac cycle [17, 19, 20]. Transthoracic echocardiography (TTE) is recommended as soon as possible in all patients after OHCA to assess PCAMD and the most common echocardiographic feature is a global myocardial hypokinesis [20, 22]. Further

manifestations are regional wall motion abnormalities and takotsubo-cardiomyopathy with apical dysfunction [20]. Coronary angiography in PCAMD does not show reduced coronary perfusion [1, 18].

During the second phase of PCAS up to 72 h after ROSC, multi-organ dysfunction ensues and an increase in intestinal permeability predisposes patients to infection [1, 11]. The onset of sepsis marks the third phase. Sepsis can then lead to entry into the fourth phase – the death of the patient [1, 11].

After ROSC, loss of vascular autoregulation of the brain leads to diminished cerebral blood flow [1]. In cases of CA with long no- or low-flow time, thrombotic processes can cause a cerebral no-reflow phenomenon. At the same time, cytotoxic brain edema develops and ROS induce necrotic and apoptotic cell death [1, 23]. This includes especially neurons in the cortex, cerebellum, thalamus and corpus striatum. Clinical manifestations of HIE are therefore coma, seizures, myoclonus and neurocognitive dysfunction to a varying extent [1].

Cranial computer tomography (cCT) is the imaging facility of choice for diagnosing HIE in the early post-cardiac arrest phase. Generalized brain edema and loss of grey-and white-matter differentiation are distinctive features [1, 24]. Magnetic resonance imaging of the brain (cMRI) can be performed in the intermediate post-cardiac arrest phase 12-72 h after ROSC and edema in diffusion-weighted imaging sequences suggests HIE [1, 22]. However, cMRI might not be feasible in case of hemodynamic instability [22].

Increasing serum neuron-specific enolase (NSE) between 48-72 h after ROSC is associated with poor outcome. Low NSE levels measured at 72 h after ROSC reduce the probability of severe HIE [22]. The 2021 ERC guideline already proposed an NSE threshold of 60 ng/ml after 48 or 72 hours, respectively, to predict poor neurological outcome [25]. The newly released 2025 guidelines additionally suggest to obtain serial NSE values at 24-72 h to determine trends and minimize confounding by hemolysis [22].

Outcome

In the EuReCa TWO study, one-third of all OHCA patients reached ROSC before transport. When analyzing only cases where CPR was undertaken by medical professionals, 64% of patients were not transported, only one-fourth of patients reached ROSC before transport and 11% of patients were transported with ongoing CPR [4]. At the time of hospital admission, 30.3% of German patients presented with ROSC [3].

In 2024, only 10.9% of all German resuscitated patients could be discharged from hospital [3]. This is similar to the average European survival-to-discharge rate of 7.5% which ranges from 3.1-35% [2]. There is great variation in survival rates not only between European countries but also globally [1, 26, 27]. This gets attributed to differences in

demographics and community response as well as inconsistent availability of specific post-resuscitation care [2].

Overall, cardiovascular causes including subsequent CA and shock are responsible for around 23% of deaths that most commonly occur during the first 72 h after ROSC [26]. Multi-organ failure consisting of infection, acute kidney injury and hypoxemia accounts for around 10% of deaths [26].

The remaining two-thirds of all fatalities after OHCA are attributed to neurological injury with persistent coma or clinical and radiological evidence of HIE [26]. Unfavorable neurological outcome with major disabilities historically occurred in more than half of all surviving patients 6 months after CA. However, as many countries have implemented withdrawal of life-sustaining treatment (WLST) guidelines, poor neurological outcome is nowadays observed in less than 10% of patients after OHCA [2, 28]. The German guideline on HIE states an incidence of 5 per 100.000 patients [23]. According to an analysis of the American “Cardiac Arrest Registry to Enhance Survival” registry, 93% of patients had mild to moderate neurologic or cognitive deficits at the time of hospital discharge [28]. Six months after OHCA, 17% of patients are fully recovered and 22% have only mild neurologic or cognitive limitations [23]. Even patients classified into the category of good neurological functioning may suffer from long-term cognitive impairments which limits societal rehabilitation [2].

The ERC provides a multimodal neuro-prognostication algorithm that is most commonly used to guide WLST decision-making [22]. It includes a clinical neurological evaluation at 72 h after ROSC focusing especially on the absence of pupillary and corneal reflexes as well as on the presence of myoclonus, an electroencephalogram (EEG) and somatosensory evoked potentials, serial measurements of biomarkers and cranial imaging [22].

Outcome prediction and post-resuscitation care

Given the high mortality and neurological morbidity rates, identifying and addressing parameters that predict outcome is a major aim of CA-related research and post-resuscitation care [22].

Several parameters of the pre-hospital phase have been identified as predictors of survival. This includes witnessed CA with immediate bystander-initiated CPR [29]. Short no-flow time (i. e. time until CPR measures are begun) and overall time to ROSC are associated with survival and good neurological outcome [30, 31].

Shockable first rhythms (ventricular fibrillation and pulseless ventricular tachycardia) are strong predictors of favorable outcome while asystole is linked to poor survival rates [29, 30]. In the EuReCa TWO study, both ROSC and survival to hospital discharge were more likely in patients with shockable rhythms (ROSC: 58% vs. 26%, survival to discharge: 24% vs. 3%) [4].

Epinephrine - a vasoconstricting agent that increases aortic diastolic pressure and improves coronary and cerebral perfusion pressures - has been an important part of resuscitation efforts for years [32]. Application of epinephrine during CPR has been found to increase the likelihood of ROSC and also to improve 30-day survival in the double-blind randomized-controlled PARAMEDIC2 trial [33]. However, there was no difference in neurological outcome between patients allocated to epinephrine and patients receiving placebo [33]. High cumulative dosages (≥3mg) of epinephrine during CPR have been linked to poor outcome [30, 34]. While interpreting these findings, it needs to be considered that when following resuscitation guidelines, the duration of CPR/time to ROSC and the dosage of administered epinephrine are interdependent [34].

ROSC at admission is a positive predictive factor as more than one-third of patients with sustained ROSC at admission and only 4% of patients admitted with ongoing CPR could be discharged in Europe in 2017 [4]. In a meta-analysis including almost 18.000 patients, ROSC before hospital admission was the strongest predictor of survival to hospital discharge [29].

Post-resuscitation care guidelines identified key aspects of therapeutic management that are associated with improved outcome [22]. Early percutaneous coronary intervention (PCI) is recommended in patients with suspected cardiac etiology and ST-elevation on electrocardiogram [22].

Management then focuses on restoring homeostasis by hemodynamic stabilization, temperature control and protective ventilation [22]. Hemodynamic management should be targeted at adequate urine output and decreasing lactate [22]. Lactate concentrations >2 mmol/l 48 h after OHCA have been found to independently predict 6 month mortality and poor neurological outcome [35]. A greater reduction of lactate within the first 12 h after OHCA has also been linked to favorable outcome [36].

For patients that remain unresponsive after ROSC, temperature control with prevention of fever for 72 h is recommended as a neuroprotective measure [22].

Galectin-3

Galectin-3 (GAL3) is a 26 kDa β-galactosidase protein belonging to the family of β-galactoside-binding lectins. GAL3 is the only subtype in chimeric form and also the only galectin that forms oligomers [37]. While the cytoplasm of epithelial and myeloid cells seems to be the main origin of GAL3 production and secretion, its expression is ubiquitous. GAL3 modulates both intracellular and extracellular pathways including the interaction between epithelium and extracellular matrix as well as apoptosis [37].

GAL3 has been observed to play a role in the innate immune response [37, 38]. It is expressed in inflammatory cells including neutrophils, monocytes and macrophages [37, 39]. It activates neutrophils, delays their apoptosis, aids opsonization of apoptotic

neutrophils and supports the phagocytosis of bacteria [40]. In addition, GAL3 increases neutrophil adhesion to endothelial cells, their extravasation and superoxide production [39]. Actively secreted by monocytes and macrophages, GAL3 serves as a chemoattractant and causes an influx of macrophages to the site of inflammation [39, 40]. In addition, GAL3 has been observed to regulate macrophage polarization into anti-inflammatory M2-macrophages facilitating the repair and remodeling processes of the infarcted myocardium after ischemic injury [38, 40].

While GAL3 is expressed in the heart under physiological conditions, significant upregulation occurs in response to a variety of stimuli. GAL3 gets secreted by macrophages and has been found to induce remodeling of the myocardium including fibrosis and collagen disposition in murine models. Consequently, it has been identified as a biomarker for inflammation in heart failure (HF) patients [41]. GAL3 was able to predict readmission to the hospital and mortality after hospitalization for acute HF [37]. In chronic HF, symptom severity was found to correlate with GAL3 concentrations [41]. In those patients, GAL3 was identified as an independent predictor of mortality especially in HF with preserved ejection fraction (HFpEF) [42].

Recently, two studies have demonstrated that admission serum GAL3 levels are higher in non-survivors and predict short- and long-term mortality as well as cerebral disability in post-cardiac arrest patients [43, 44]. Both studies identified cut-off concentrations for GAL3 for prediction of mortality at 26.6 ng/ml and 26.3 ng/ml, respectively [43, 44].

Study objectives

Based on the aforementioned literature, this study has three main objectives: first, to establish the time course of serum GAL3 regulation during the early post-resuscitation phase; second, to confirm the prognostic value of GAL3 measurements for survival to hospital discharge after resuscitation; and third, to provide insight into the association between GAL3 levels and characteristics of PCAS.

Summary of methods

For all aspects of these methods, detailed information is provided in the original publication.

This is a prospective, two-center cohort study performed at the Department of Cardiology, University Hospital of Oldenburg, Germany and the Department of Cardiology and Angiology at the University Hospital of Freiburg, Germany. The protocol was approved by the ethics committee of the University of Oldenburg (No. 2020-021) and the University of Freiburg (No 239/16) and corresponds to the Declaration of Helsinki. The study protocols for each center are available at the German Clinical Trials Register (DRKS00020250, DRKS00009684). Informed consent was obtained from OHCA patients who survived to discharge with favorable neurological outcome or from their next of kin after personal contact. Upon admission to hospital, comatose OHCA patients who were older than 18 years and reached ROSC after ≥5 minutes of CPR were eligible for inclusion. OHCA patients following trauma, pregnant patients and those with end-stage kidney disease (glomerular filtration rate <15ml/min/1.73m^2) were excluded [45].

A control group of 39 patients with known coronary artery disease (CAD) who were admitted for scheduled coronary angiography was formed.

Outcome measures

The relationship between GAL3 levels and the following key features of PCAS was investigated in the original publication: (1) in-hospital mortality, (2) signs of cerebral edema on cCT, (3) lactate on admission, (4) duration of vasopressor and inotropic therapy (5) lactate clearance and (6) serum IL-6 levels.

Further parameters that are not presented in the original publication are described here:

(1) To identify potential influences of OHCA-precipitating pathologies on GAL3 levels, the etiology of OHCA was defined after consultation with the intensive care physician, interventional cardiologist and emergency physician. Primary cardiac causes of OHCA (e.g. myocardial infarction, arrhythmogenic cardiomyopathies, myocarditis) were distinguished from primary non-cardiac causes of OHCA (e.g. electrolyte disturbances, acute respiratory failure, acute hemorrhage, acute neurological disorders, intoxication and others).

(2) To further characterize neurological outcome, clinical neurological outcome and NSE were evaluated. Clinical neurological outcome at hospital discharge was described based on the Cerebral Performance Categories (CPC). The CPC scale is well established to describe neurological outcome after CA [46]. It allows for classification of patients into five categories ranging from good cerebral performance to brain death [47]. An overview of the categories is provided in the

Appendix (Supplement I). It is customary to define two groups: favorable outcome with CPC 1-2 and unfavorable outcome including CPC 3-5 [48]. The CPC is often determined by hospital chart review and inter-rater agreement has been shown to be acceptable [48, 49]. In this cohort, CPC was determined after personal contact and chart review.

As an established biomarker to predict neurological outcome after OHCA, NSE was measured at 48 h after ROSC. In accordance with ERC guidelines, a cut-off of NSE >60 ng/ml 48 h after ROSC was used to identify patients with poor neurological prognosis [22]. NSE levels are potentially higher in patients that receive extracorporeal life-support (ECLS) as they are influenced by hemolysis [50]. Therefore, NSE analyses excluding patients that received ECLS were performed.

(3) To assess hemodynamic instability and cardiac function in more detail, patients received TTE to evaluate LVEF within the first 24 h after admission. Two LVEF groups were formed to differentiate patients with severely reduced LVEF ≤30% and those with LVEF >30%. As a global marker of heart failure, n-terminal pro brain natriuretic peptide (NT-proBNP) was measured on day 0 and 2 after OHCA and correlated to GAL3 serum levels.

Blood sampling and biomarker measurements

For patients with OHCA, the first venous blood sample was collected within 6 h after ROSC. Follow-up blood sampling was performed on day 2 as part of the routine laboratory work-up. NSE was measured at individual timepoints for each patient at 48 h after ROSC [22]. In CAD controls, blood samples were collected immediately following coronary angiography**.**

All presented serum parameters except for GAL3 were measured by the Department of Clinical Chemistry and Laboratory Medicine at the University Hospital Oldenburg and the University Hospital Freiburg, respectively. GAL3 was measured in serum using the “Quantikine ELISA Human Galectin-3 Immunoassay” (DGAL30, USA R&D Systems Inc., Minneapolis, USA). The analyses were conducted as described in the manufacturer’s protocol.

Statistical analyses

Continuous variables were tested for normal distribution with Shapiro-Wilk’s test and are presented as median and interquartile range (IQR). Continuous variables were compared using Mann-Whitney-U-test or Wilcoxon signed-rank test. Categorical variables are presented as counts and percentages and differences were tested with the

chi-square (Chi^2) test or Fisher's exact test. Correlations between metric variables were analyzed by Spearman's rank correlation and the coefficient rho (r) is reported.

The serial determination of GAL3 within each patient allowed for analyzing associations with dichotomous outcome variables by repeated measures linear mixed models. GAL3 was the dependent variable. Fixed effects included time, the respective outcome measure and their interaction term while patients were included as a random effect. For each model, post-hoc pairwise comparisons were conducted using Šidák's test to differentiate if differences in GAL3 with regard to the respective outcome variable could be attributed to a specific time point of GAL3 measurement. To assess the value of GAL3 for outcome prediction, receiver operating characteristic (ROC) analyses were performed. Results are reported as area under curve (AUC). The optimal cut-off was determined with the maximized Youden index (YI). The optimal cut-off value was then included in a univariate logistic regression model as an independent categorical predictor. Results are reported as Odds Ratio (OR) with 95% confidence interval (CI). All tests were two-sided and statistical significance was defined as $p<0.05$ unless otherwise specified. Statistical analyses were performed using IBM SPSS Statistics 30 (IBM, Armonk, USA). Plotting and mixed models were done with GraphPad Prism 10 (GraphPad Software, San Diego, USA).

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Original Article

Galectin-3 as a marker to characterize post-cardiac arrest syndrome in initially survived out-of-hospital cardiac arrest: a prospective two-center study

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Abstract

Background: Survivors after out-of-hospital cardiac arrest (OHCA) experience post-cardiac arrest syndrome (PCAS), which encompasses cerebral edema, hemodynamic instability and systemic inflammation and causes high in-hospital mortality rates. Galectin (GAL) 3 is a predictor of mortality and unfavorable neurological outcome following OHCA. This study aims to investigate the relationship between GAL3 levels and key features of PCAS including in-hospital mortality, cerebral edema, post-cardiac arrest shock and systemic inflammation in OHCA patients.

Methods: This prospective, two-center study included 71 adults after non-traumatic OHCA. Blood samples were taken on hospital admission (day 0) and day 2 after return of spontaneous circulation (ROSC). Serum GAL3 concentrations were quantified by enzyme-linked immunosorbent assay and compared with serum levels of 39 patients with coronary artery disease (CAD).

Results: Serum GAL3 levels were highest on day 0 and declined on day 2 after ROSC to levels comparable to CAD controls. GAL3 levels were higher in non-survivors at both time- points. Admission GAL3 concentrations positively correlated with lactate on admission, a marker for no-flow/low-flow time and were elevated in patients with cerebral edema on cerebral computed tomography. Furthermore, admission GAL3 was higher in patients with inadequate lactate clearance and GAL3 levels on day 2 were significantly elevated in OHCA patients who required prolonged vasopressor/inotropic medication, both indicators of persistent hypoperfusion and shock. Moreover, a positive correlation was observed between GAL3 and interleukin-6 on admission.

Conclusion: Serum GAL3 levels are associated with in-hospital mortality and distinct features of PCAS including cerebral edema, persistent shock and systemic inflammation following OHCA.

German Clinical Trials Register No. DRKS00020250; DRKS00009684.

Keywords: OHCA, Galectin-3, In-hospital mortality, PCAS, Cerebral edema, Shock, Interleukin-6

Background

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in both Europe and the United States.[1 5] Despite advances in management, the prognosis for patients who initially survive an OHCA remains poor.[1,3 5] Approximately 8 % of OHCA patients are discharged from hospital alive.[2,3,6]

The primary factor contributing to a poor outcome after return of spontaneous circulation (ROSC) is the development of post-cardiac arrest syndrome (PCAS). PCAS is characterized by hypoxic-ischemic encephalopathy (HIE), post-cardiac arrest myocardial dys-

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function, hemodynamic instability and a systemic inflammatory response.[3,7] This syndrome arises as a consequence of whole-body ischemia/reperfusion (I/R) injury during prolonged resuscitation.[8] The severity of PCAS is largely determined by the duration of global ischemia and the subsequent release of inflammatory mediators such as interleukins (IL) and reactive oxygen species during reperfusion.[1]

Galectin-3 (GAL3) is a 26 kDa β-galactosidase protein belonging to the family of β-galactoside binding lectins. It is expressed in inflammatory cells including neutrophils, monocytes and macrophages[9,10] and has been observed to play a role in the innate immune response.[9 12] Recently, two studies have demonstrated that admission serum GAL3 levels were higher in non-survivors and predicted short- and long-term mortality, as well as cerebral disability in post-cardiac arrest patients.[13,14] The role of GAL3 in the early phase after resuscitation remains unclear. This study explores the regulation of serum GAL3 at two time points in the early post-resuscitation phase and provides insight into the association between GAL3 levels and characteristics of post-cardiac arrest syndrome (PCAS).

Methods

This is a prospective, two-center cohort study performed at the Department of Cardiology, University Hospital of Oldenburg, Germany and Department of Cardiology and Angiology at the University Hospital of Freiburg, Germany between May 2016 and December 2021. The protocol was approved by the ethics committee of the University of Oldenburg (No. 2020-021) and the University of Freiburg (No 239/16) and corresponds to the declaration of Helsinki. The study protocols for each center are available at the German Clinical Trials Register (DRKS00020250, DRKS00009684). Informed consent was obtained from resuscitated non-traumatic OHCA patients who survived to discharge with favorable neurological outcome or from their next of kin after personal contact. Upon admission to hospital, comatose OHCA patients who were older than 18 years and reached ROSC after ≥5 min of cardiopulmonary resuscitation (CPR) were eligible for inclusion. OHCA patients following trauma, pregnant patients and those with end-stage kidney disease (glomerular filtration rate <15 ml/min/1.73 m^2) were excluded as impaired renal function increases GAL3 levels.[15] One patient diagnosed with acquired immunodeficiency syndrome (AIDS) was excluded, as elevated GAL3 serum levels have been reported in human immunodeficiency virus (HIV) patients even when viral RNA is undetectable.[16] In addition, this measure aimed to minimize any potential infection risk to blinded study personnel.

A control group of 39 patients with known coronary artery disease (CAD) was formed. As CAD patients are similar in age, sex and cardiovascular comorbidities to OHCA patients and CAD assessment requires coronary angiography, they form an adequate control group.[1,17 19] Information on patient management is provided within the supplement (Additional file 1).

Outcome measures

The relationship between GAL3 levels and the following key features of PCAS was investigated: (1) in-hospital mortality, (2) signs of cerebral edema on cranial computed tomography (cCT), (3) lactate on admission, (4) duration of vasopressor and inotropic therapy (5) lactate clearance and (6) serum IL-6 levels.

Patients underwent cCT 48–72h after ROSC. cCT scans were evaluated for signs of cerebral edema by senior consultants of diagnostic radiology. The relationships between GAL3 and admission lactate levels and lactate clearance were also assessed. Inadequate lactate clearance was defined as a lactate concentration ≥2 mmol/L on day 2 after ROSC.[20] To assess hemodynamic instability, the patients' need for different inotropic/vasopressor medications throughout the intensive care unit (ICU) stay was evaluated. To assess the relationship between GAL3 levels and the inflammatory response following OHCA, the extent of inflammation was measured by serum levels of IL-6.[21 27]

Blood sampling and biomarker measurements

For patients with OHCA, the first venous blood sample was collected from a venous catheter within 0–6h after ROSC in the intensive care unit (day 0). To assess GAL3 regulation during the intermediate phase of PCAS – beyond the immediate effects of ischemia/reperfusion injury (day 0)[1] – follow-up blood sampling was routinely performed on day 2 as part of the early morning laboratory work-up in the ICU, typically between 5:00 and 6:00 a.m. NSE was measured at individual timepoints for each patient at 48h after ROSC to ensure optimal timing for neuroprognostication.[3] A cut-off of >60 ng/ml is considered indicative of poor neurological outcome.[3] In CAD controls, blood samples were collected by research staff immediately following coronary angiography. After collection and centrifugation, the isolated serum was immediately stored at −21 °C until it was shipped to the central laboratory for ELISA measurements. Serum GAL3 was measured using the Quantikine ELISA Human Galectin-3 Immunoassay (DGAL30, USA R&D Systems Inc., Minneapolis, MN, USA). IL-6 and NSE were measured by the respective hospitals' Department of Clinical Chemistry and Laboratory Medicine. Further information is provided in Additional file 2.

Statistical analyses

Continuous variables were tested for normal distribution with Shapiro-Wilk's test and are presented as median and interquartile range (IQR). Continuous variables were compared using Mann-Whitney-*U* test or Wilcoxon signed-rank test. Categorical variables are presented as count and percentages and differences were tested with the chi-square (Chi^2) test or Fisher's exact test. Correlations between metric variables were analyzed by Spearman's rank correlation and the coefficient rho (*r*) is reported.

The serial determination of GAL3 within each patient allowed for analyzing associations with dichotomous outcome variables by repeated measures linear mixed models. GAL 3 was the dependent variable. Fixed effects included time, the respective outcome measure and their interaction term while patients were included as a random effect. The model was estimated using REML. Model results were reported after checking for underlying assumptions (normal distribution of residuals, homoscedasticity). For each model, post-hoc pairwise comparisons were conducted using Šidák's test to differentiate if differences in GAL3 with regard to the respective outcome variable could be attributed to a specific time point of GAL3 measurement. To assess the value of GAL3 for outcome prediction, receiver operating characteristic (ROC) analyses were performed. Results are reported as area under curve (AUC). The optimal cut-off was determined with the maximized Youden index. The optimal cut-off

value was then included in a univariate logistic regression model as an independent categorical predictor. Results are reported as Odds Ratio (OR) with 95 % CI. All tests were two-sided and statistical significance was defined as $p < 0.05$ unless otherwise specified. Statistical analyses were performed using IBM SPSS Statistics 29 (IBM, Armonk, NY, USA). Plotting and mixed models were done with GraphPad Prism 10 (GraphPad Software, San Diego, CA, USA).

Results

Seventy-one patients after non-traumatic OHCA were included for analyses. Details on patient in- and exclusion are provided in the supplement (Additional file 3). Patient characteristics are shown in Table 1. The average age was 64 (IQR 55.8–74.5) years and 71.8 % ($n = 51$) of patients were male. Median estimated no-flow time was 2.5 (IQR 0.0–10.0) min and median time to ROSC was 20.0 (IQR 15.0–30.5) min. Shockable rhythms were observed in 52.1 % ($n = 37$) of OHCA patients. In-hospital mortality was 60.6 % ($n = 43$). The median time to death was 3 (IQR 1–7) days.

Serum GAL3 levels on admission (day 0) were significantly higher than on day 2 after ROSC ($p < 0.001$; Fig. 1, Table 2). GAL3 levels at the time of hospital admission were significantly higher than in CAD controls, while GAL3 levels on day 2 were comparable to those measured in the CAD group (Fig. 1, Table 2). GAL3 levels showed significant differences between survivors and non-survivors on admission ($p = 0.015$; Table 2). A cut-off of GAL3 on day 0 > 37.48 ng/ml was identified to predict death with a sensitivity of 70.0 % and a specificity of 73.1 % (Univariate logistic regression analysis: OR 9.45 [2.60–34.34], $p < 0.001$; Fig. 2).

GAL3 levels on admission were significantly higher in OHCA patients with cerebral edema on cCT ($p = 0.019$; Table 3), which rep-

Table 1 – Baseline characteristics and survival status after OHCA.

	Survivors $n = 28$	Non-survivors $n = 43$	p
Age [years], median (IQR)	63.0 (48.5–75.5)	66.0 (60.0–81.0)	0.063
Male sex, *n* (%)	22 (75.6)	29 (67.4)	0.420
Comorbidities, *n* (%)			
Coronary artery disease	19 (67.9)	18 (41.8)	0.052
Arterial hypertension	16 (57.1)	25 (58.1)	1.000
Chronic heart failure	5 (17.9)	4 (9.3)	0.469
Diabetes mellitus	3 (10.7)	8 (18.6)	0.506
COPD	1 (3.6)	5 (11.6)	0.389
Cardiac cause of OHCA, *n* (%)	23 (82.1)	23 (53.5)	**0.039**
First documented rhythm, *n* (%)			**<0.001**
Shockable rhythm	22 (75.6)	15 (34.9)	
Asystole	1 (3.6)	18 (41.8)	
Pulseless electrical activity	5 (17.9)	10 (23.3)	
Time to CPR (no-flow time) [min], median (IQR)	1.0 (0.0–2.0)	6 (1.0–10.0)	**0.002**
Time to ROSC [min], median (IQR)	15.0 (12.0–25.0)	20 (10.0–40.0)	0.267
Left ventricular dysfunction on admission, *n* (%)			1.000
LVEF ≤30 %	9 (32.1)	13 (30.2)	
LVEF >30 %	14 (50.0)	22 (51.2)	
No echocardiography available	5 (17.9)	8 (18.6)	
ECLS, *n* (%)	3 (10.7)	6 (14.0)	1.000
Application of vasopressors, *n* (%)	27 (96.4)	38 (88.4)	0.641
Application of inotropics, *n* (%)	9 (32.1)	14 (32.6)	1.000
Vasopressors/inotropics >3 days, *n* (%)	15 (53.6)	16 (37.2)	0.325
Lactate on admission [mmol/L], median (IQR)	4.3 (2.0–6.3)	7.4 (4.0–12.0)	**0.001**
Adequate lactate clearance, *n* (%)	19 (67.9)	11 (25.6)	**0.009**
Cause of death	/		
Hypoxic-ischemic encephalopathy, *n* (%)		26	
Cardiovascular, *n* (%)		11	
Other (e.g. sepsis, respiratory), *n* (%)		6	
CPC			**<0.001**
CPC 1–2, *n* (%)	20 (71.4)	0 (0)	
CPC 3–5, *n* (%)	8 (28.6)	43 (100.0)	
NSE 48h [ng/ml], median (IQR)*	47.4 (29.0–90.8)	67.4 (27.0–180.0)	0.361
cCT obtained, *n* (%)	23 (79.3)	38 (88.4)	0.323
TTM to 33 °C for 24 h, *n* (%)	23 (82.1)	31 (72.1)	0.765

Data are presented as median and IQR. Survival status is based on survival to hospital discharge. The *p*-value represents comparison between groups. $p < 0.05$ was considered significant.

CAD coronary artery disease, *cCT* cranial computed tomography, *COPD* chronic obstructive pulmonary disease, *CPC* cerebral performance category, *CPR* cardiopulmonary resuscitation, *ECLS* extracorporeal life support, *IQR* interquartile range, *LVEF* left ventricular ejection fraction, min minutes, *NSE* neuron-specific enolase, *OHCA* out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, *TTM* targeted temperature management.

* ECLS patients were excluded from this analysis.

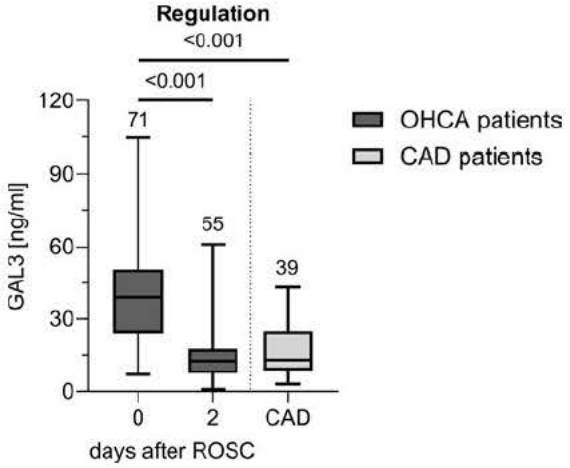

Fig. 1 – *Regulation of serum GAL3 levels in patients after OHCA.* Concentrations of GAL3 were highest on admission and showed a significant decrease within 48h after ROSC. Boxplots show median with IQR, whiskers denote range. Digits above whiskers show number of patients in each group. Between-day differences tested with Wilcoxon signed-rank test. Mann-Whitney-*U* test performed for between-group comparison. $p < 0.05$ was considered significant. *CAD* coronary artery disease, *GAL3* Galectin-3, *IQR* interquartile range, *OHCA* out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation.

resents the morphological correlate of HIE and reflects the extent of cerebral injury following I/R. Median blood lactate level on admission was 5.6 (IQR 2.2–7.7) mmol/L and decreased on day 2 to 1.7 (IQR 1.1–3.1) mmol/L. Serum GAL3 levels at admission showed a positive correlation to lactate on admission ($r = 0.276$, $p = 0.036$), a surrogate marker of no-flow and low-flow time during CPR.

31.0 % ($n = 22$) of OHCA patients required vasopressor/inotropic medication for a maximum duration of three days (≤3 days), whereas 43.7 % ($n = 31$) of patients required such therapy for at least four days (>3 days) throughout the post-resuscitation period (Table 3). GAL3 levels on day 2 were significantly elevated in patients who required prolonged vasopressor/inotropic support in comparison to those who needed shorter vasopressor/inotropic support for a period of ≤3 days ($p = 0.030$; Table 3).

Adequate lactate clearance was observed in 42.3 % ($n = 30$) patients after OHCA, while 35.2 % ($n = 25$) of patients showed lactate ≥2 mmol/L on day 2 after ROSC (inadequate lactate clearance). As an indicator of hemodynamic stabilization, adequate lactate clearance was associated with survival to hospital discharge in logistic regression analyses (OR 4.44 [1.41–13.97], $p = 0.011$). Serum GAL3 levels at admission were significantly higher in patients with inadequate lactate clearance, indicating that GAL3 levels are higher in OHCA patients with hemodynamic instability ($p = 0.014$; Table 3).

In this OHCA cohort, IL-6 was already elevated on admission and increased further on day 2 after OHCA (day 0: 120.8 [IQR 34.6–321.1] ng/L; day 2: 200.1 [95.7–592.9] ng/L). A positive correlation was observed between GAL3 on day 0 and IL-6 on admission but not on day 2 (day 0: $r = 0.393$, $p = 0.001$; day 2: $r = 0.133$, $p = 0.378$).

Discussion

This study presents novel findings on the regulation of serum GAL3 levels in the early phase after ROSC and its diagnostic and prognostic value after initial OHCA survival. Key observations include: First, serum GAL3 levels on hospital admission after OHCA are significantly higher than both levels measured on day 2 and those observed in patients with CAD (Fig. 1). Second, elevated serum GAL3 levels on hospital admission are a predictor of in-hospital mortality after OHCA (Fig. 2). Third, GAL3 levels on admission are elevated in OHCA patients with cerebral edema on cCT, the morphological correlate of hypoxic-ischemic encephalopathy and showed a positive correlation with lactate on admission (Table 3). Fourth, higher GAL3 levels are associated with hypoperfusion and post-cardiac arrest shock reflected by prolonged need of vasopressor/inotropic support and inadequate lactate clearance (Table 3). Fifth, GAL3 on admission correlates with IL-6 on admission, an independent predictor of mortality and PCAS severity.[22,23,27,28]

Upregulation of GAL3 has been observed in a variety of critically-ill patients on ICU presenting with sepsis, trauma or COVID-19.[29 31] In addition, elevation of GAL3 was reported in patients with severe heart failure with need for mechanical circulatory support and acute myocardial infarction (AMI) with hemodynamic instability.[32,33] Two studies have previously revealed GAL3 elevation on hospital admission in serum of OHCA patients.[13,14] The present study is the first to

Table 2 – Serum concentrations of GAL3 for OHCA patients and CAD controls.

	GAL3 [ng/ml], median (IQR)		
	OHCA ($n = 71$)		CAD ($n = 39$)
	day 0	day 2	
Total	39.19 (24.10–50.78)	12.63 (7.53–17.54)	13.0 (8.72–25.01)
Survival status			
Survivors ($n = 28$)	24.13 (15.89–42.47)	10.02 (5.71–15.54)	13.0 (8.72–25.01)
Non-survivors ($n = 43$*)	43.88 (31.31–57.77)	16.13 (9.98–21.35)	/
p**	**0.015**	0.079	

Šidák's test was used to control for multiple testing; $p < 0.05$ was considered significant. *CAD* coronary artery disease, *GAL3* Galectin-3, *IQR* interquartile range, *OHCA* out-of-hospital cardiac arrest.

* Number of patients on day 0 (day of admission); non-survivors day 2 $n = 27$.

** The presented p-values are results of post-hoc multiple comparison tests on linear mixed models.

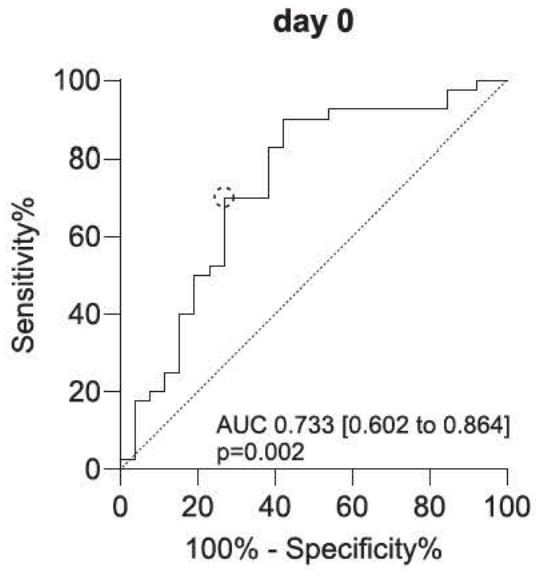

Fig. 2 – *GAL3 levels on admission are higher in non-survivors after OHCA.* ROC-analysis shows good classification for GAL3 levels on admission. Statistics of analysis given within the figure. To determine the optimal cut-off which maximizes sensitivity and specificity, Youden's Index was calculated (YI = 0.43, shown as dotted circle). $p < 0.05$ was considered significant. *AUC* area under curve, *GAL3* Galectin-3, *OHCA* out-of-hospital cardiac arrest, *ROC* receiver-operating characteristic.

analyze the temporal profile of GAL3 beyond admission during the early post-resuscitation period (Fig. 1). GAL3 levels peaked on admission after OHCA and declined on day 2 to levels comparable to those observed in CAD controls suggesting that GAL3 down-regulation is linked to whole-body reperfusion. This pattern aligns with findings in stroke and ST-elevation myocardial infarction patients, where GAL3 levels peaked during ischemia and declined after reperfusion.[34,35] Similarly, in our OHCA cohort, the initial GAL3 peak likely reflects no-flow/low-flow ischemia during resuscitation, while the subsequent decrease indicates reperfusion. Supporting this, patients with persistent ischemia from post-cardiac arrest shock showed higher GAL3 levels on day 2, along with ongoing vasopressor use and impaired lactate clearance (Table 3).[36–38]

Overall outcome prediction remains a central challenge during the early post-resuscitation phase.[3] Two previous studies have suggested a possible prognostic role of admission GAL3 levels in OHCA.[13,14] In one prospective multicenter study, serum GAL3 levels at hospital admission following OHCA were higher in non-survivors and concentrations >26.6 ng/ml were identified as an independent risk factor for all-cause mortality after 4 weeks as well as 5 months of follow-up.[13] A recent study has indicated that elevated GAL3 levels (>26.3 ng/ml) at the time of admission can serve as a predictor of mortality after 5.7 years in OHCA survivors.[14] The present study identified an optimal cut-off value to predict in-hospital mortality of ≥37.48 ng/ml (Fig. 2). Therefore, our results are in line with the available literature suggesting that GAL3 levels on admission may serve as a potential biomarker that might contribute to prognostication after OHCA.

The majority of fatalities after OHCA are attributed to HIE.[1,39,40] After initial stabilization of an OHCA patient, a multimodal algorithm to evaluate the extent of HIE is recommended by the European Resuscitation Council (ERC) guidelines.[3] In the present study, GAL3 on admission demonstrated neither an association with NSE after 48h, nor was there a correlation with neurological outcomes as determined by Cerebral Performance Categories (CPC) at the time of hospital discharge (Additional files 4 and 5). However, serum GAL3 levels were found to correlate with the presence of cerebral edema as depicted on cCT and with lactate on admission, which has been previously identified as a predictor of poor neurological outcome.[20,36,41,42] A recent analysis has identified GAL3 on admission as a predictor of long-term cerebral disability assessed by CPC at 5.7 years after OHCA.[14]

Post-resuscitation shock occurs in up to 60 % of OHCA patients, contributes to multi-organ failure and poor prognosis and requires early and aggressive management.[3,39,40,43] The complex pathophysiology of post-resuscitation shock includes vasoplegia and myocardial dysfunction due to systemic I/R injury and sepsis-like

Table 3 – Serum levels of GAL3 and key features of PCAS.

	GAL3 [ng/ml], median (IQR)	
	day 0	day 2
Brain edema on cCT		
No brain edema ($n = 44$)	39.18 (24.24–48.79)	14.03 (7.07–21.52)
Brain edema ($n = 16$)	50.21 (27.72–101.93)	12.32 (6.89–17.66)
p^*	**0.019**	0.678
Duration of vasopressor/inotropic support		
≤3 days ($n = 22$)	40.98 (25.06–50.23)	10.60 (4.43–15.95)
>3 days ($n = 31$)	31.23 (23.84–59.79)	13.98 (9.03–21.95)
p^*	0.996	**0.030**
Lactate clearance		
Adequate ($n = 30$)	31.23 (23.84–21.49)	10.09 (7.14–16.49)
Inadequate ($n = 25$)	41.36 (21.10–73.02)	14.07 (9.03–21.38)
p^*	**0.014**	0.419

Šidák's test was used to control for multiple testing; $p < 0.05$ was considered significant. *cCT* cerebral computed tomography, *GAL3* Galectin-3, *IQR* interquartile range, *OHCA* out-of-hospital cardiac arrest, *PCAS* post-cardiac arrest syndrome.

* The presented *p*-values are results of post-hoc multiple comparison tests on linear mixed models.

syndrome, both features of post-cardiac arrest syndrome (PCAS).[1,3] In this cohort, GAL3 levels remained higher in patients with prolonged vasopressor requirements and inadequate lactate clearance on day 2 after ROSC (Table 3). This identifies GAL3 as a novel potential marker of prolonged hypoperfusion and shock after cardiac arrest. Supporting this findings, GAL3 concentrations were observed to correlate with need for inotropic medication in acute heart failure, AMI and a cohort of patients after left-ventricular assist device implantation.[33,44,45]

In recent years, evidence on lactate clearance as a surrogate parameter for resolution of hypoperfusion and shock has emerged.[36] Interpretation of a singular lactate value is difficult as lactate levels are representative of both lactate build-up due to e.g. tissue hypoxia during resuscitation but are also influenced by post-cardiac arrest aspects that hinder lactate elimination processes.[36 38] Lactate clearance within 3–48h after admission predicts short-term and 30-day survival following ROSC.[20,37,46 49] In line with these reports, this study shows that adequate lactate clearance is associated with survival to hospital discharge and GAL3 levels are higher in patients with inadequate lactate clearance (Table 3).

The early post-resuscitation phase involves a systemic inflammatory response with elevated cytokines such as IL-6 and TNF-α.[21,50,51] In this cohort, IL-6 increased on day 2. Elevated IL-6 within 72h post-ROSC has been linked to organ dysfunction, PCAS severity and higher mortality,[22,23,27,28] as well as endothelial activation and vasopressor need.[24,25] IL-6 is induced via toll-like receptor (TLR) signaling[52] and GAL3 may contribute by activating TLR4, thereby promoting IL-6 production.[53] In this study, admission GAL3 correlated with IL-6 on day 0, supporting its role in triggering inflammation via innate immune activation.[12,54] GAL3 enhances neutrophil function and macrophage recruitment and polarization after ischemic injury.[12] These observations, in line with previous studies, suggest a possible involvement of GAL3 in the inflammatory response following cardiac arrest.

Limitations

Despite the prospective, two-center study design, the present study has several limitations and the results should be applied carefully to other situations and populations. Due to early mortality, not all outcome measures could be assessed in the entire cohort (n = 71). Specifically, brain edema could be evaluated in 60 patients, lactate clearance in 55 patients, and the need for prolonged vasopressor or inotropic support in 53 patients (Additional file 6). These missing data may introduce selection bias and should be considered when interpreting the subgroup results. The proportion of survivors (39 %) in this study is considerably higher than reported in international studies and the German resuscitation register with survival rates below 20 %.[1,2,39,55] The rather low mortality can be attributed, at least in part, to the high percentage of patients with shockable rhythms (52.1 %) and cardiac cause (64.8 %) as a trigger for cardiac arrest which is known to be associated with better outcome.[56] A number of patients died after life-sustaining therapy was withdrawn for poor neurological prognosis after neuroprognostication in line with ERC guidelines. These patients cannot be differentiated from cases that fulfilled brain death criteria.

As is inherit to any observational study, we cannot prove a causal relationship but only describe the association between GAL3 and outcome parameters. It cannot be excluded that, at least in some of the patients, GAL3 levels were already elevated before OHCA due to pre-existing comorbidities. In this cohort, subgroup analyses show that GAL3 levels are higher in non-survivors with prior ischemic heart disease, arterial hypertension and diabetes mellitus (data not shown). However, the respective number of patients analyzed in each subgroup was small, hence, these results should be re-evaluated in larger patient settings. Most of the resuscitated patients were undergoing targeted temperature management (TTM). We cannot exclude possible effects of TTM on GAL3 levels.

Conclusions

The present study demonstrates upregulation of GAL3 in the post-resuscitation period. GAL3 levels on admission are a possible predictor of in-hospital mortality after OHCA and are associated with cerebral edema and IL-6 driven inflammation. Moreover, elevated GAL3 levels were associated with ongoing post-cardiac arrest shock.

CRediT authorship contribution statement

Swantje Nickelsen: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Eleonore Grosse Darrelmann:** Writing – review & editing, Resources, Investigation. **Lea Seidlmayer:** Writing – review & editing, Resources, Investigation. **Katrin Fink:** Writing – review & editing, Conceptualization. **Simone Britsch:** Writing – review & editing, Supervision. **Daniel Duerschmied:** Writing – review & editing, Supervision. **Ruediger E. Scharf:** Writing – review & editing, Supervision. **Albrecht Elsaesser:** Visualization, Conceptualization. **Thomas Helbing:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: “D. Duerschmied is supported by the DFG (CRC1366 B08, project number 394046768, and CRC1425 P07, project number 422681845) and the DZHK (MaBo-05).”.

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Appendix A. Supplementary material

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Original publication - Additional files

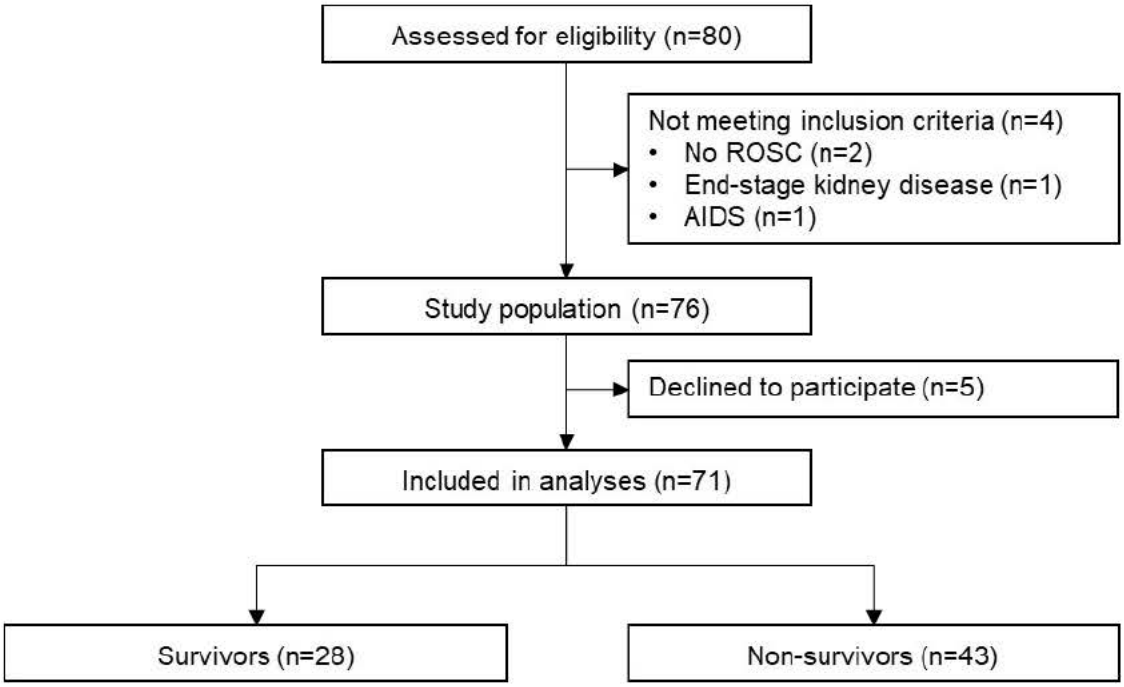
Additional file 1 Patient management

The centers at Oldenburg and Freiburg recruited 25 and 46 patients, respectively. All patients were admitted to the medical ICU. Invasive hemodynamic monitoring of patients was performed with a pressure catheter in the radial artery. Crystalloid fluids were administered in all patients to achieve general treatment goals for central venous pressure (CVP) of 10-15 mmHg to optimize right heart filling pressure and urine output >1.5 ml/kg/h. The hemodynamic target was mean arterial pressure >65 mmHg to ensure sufficient organ perfusion. Vasopressor/inotropic agents were used if volume substitution alone did not result in adequate hemodynamics or was not feasible. Percutaneous coronary intervention (PCI) was performed if a patient presented with ST-segment elevation on electrocardiogram (ECG) or at the treating physician's discretion. Targeted temperature management (TTM) after ROSC was applied according to ERC guidelines at the time of patient inclusion [25]. Withdrawal of life-sustaining treatment decisions for poor neurological outcome were made by senior consultants of neurology and intensive care medicine in accordance with the ERC guideline recommendations [25].

Additional file 2 Blood sampling and biomarker measurements

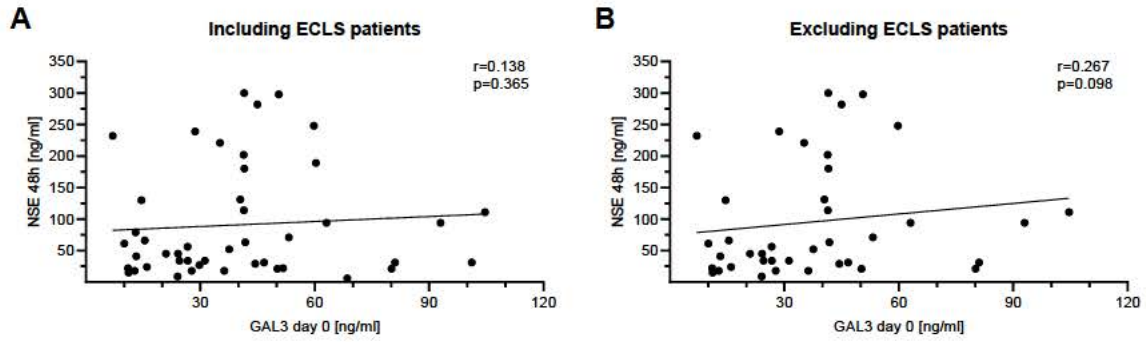
After sample collection and centrifugation, the isolated serum was stored at -21°C until it was shipped to the central laboratory, where it was further stored at -80°C. At both centres, samples were thawed immediately before enzyme-linked immunosorbent assay (ELISA) measurements and were not subjected to repeated freeze-thaw cycles. Serum GAL3 was measured using the Quantikine ELISA Human Galectin-3 Immunoassay (DGAL30, USA R&D Systems Inc., Minneapolis, USA). Intra-assay and inter-assay precision were 3.8% and 6.3%, respectively. Analyses were performed according to the manufacturer's protocol and personnel were blinded to all clinical information. All samples were analyzed in duplicate.

Additional file 3 Study flow diagram



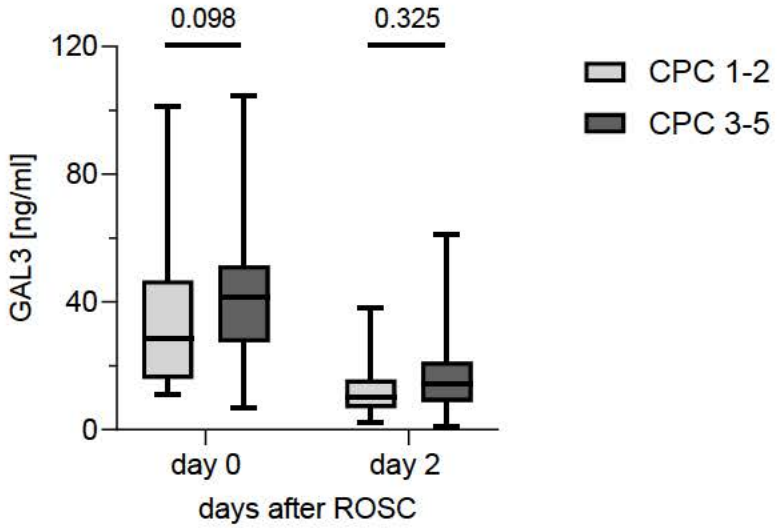
Legend: Flowchart of the study population available for analyses. The AIDS patient was excluded to prevent confounding due to elevated GAL3 levels in HIV, even in the absence of detectable viral RNA. *AIDS* acquired immune deficiency syndrome, *GAL3* galectin-3, *HIV* human immunodeficiency virus, *ROSC* return of spontaneous circulation

Additional file 4 Correlation of GAL3 on admission and NSE at 48h in patients after OHCA



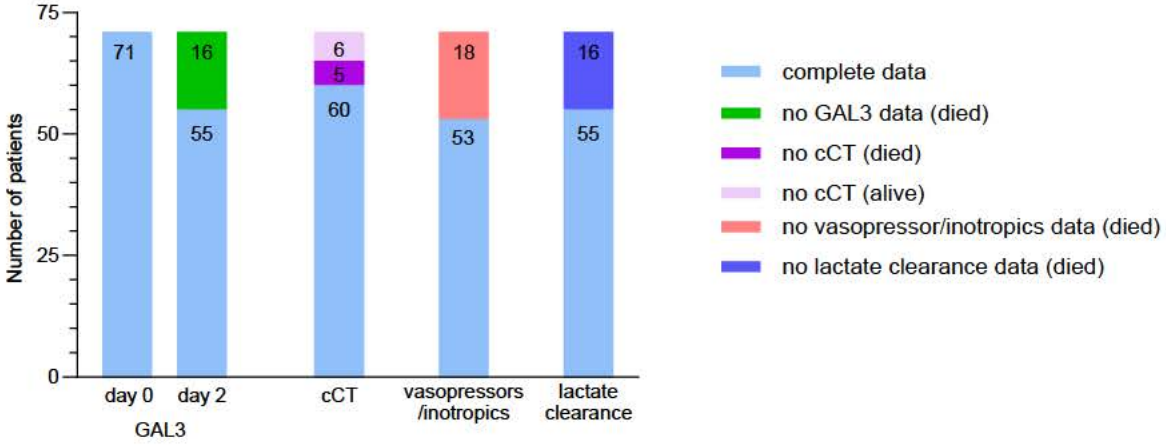
Legend: GAL3 on admission did not correlate with NSE at 48h after ROSC (A). When ECLS patients were excluded to account for potential confounding by hemolysis, a trend towards a significant correlation between admission GAL3 and NSE after 48h was observed (B). Results of Spearman correlation coefficient r and respective p-value are presented within the figure. $p<0.05$ was considered significant. *ECLS* extra-corporeal life support, *GAL3* galectin-3, *IQR* interquartile range, *NSE* neuron-specific enolase, *OHCA* out-of-hospital cardiac arrest

Additional file 5 GAL3 and neurological outcome in patients after OHCA



Legend: GAL3 was not significantly higher in patients with poor neurological outcome. Boxplots show median with IQR, whiskers denote range. The presented p-values are results of post-hoc multiple comparison tests on linear mixed models and Šidák's test was used to control for multiple testing; $p<0.05$ was considered significant. *CPC* cerebral performance category, *GAL3* galectin-3, *IQR* interquartile range, *OHCA* out-of-hospital cardiac arrest

Additional file 6 Missing data



Legend: Bar chart illustrating the number of patients available for analyses for each outcome measure. The exact number of patients is given within the bar. *cCT* cranial computed tomography, *GAL3* galectin-3

Further results not presented in the original publication

Serum GAL3 levels and OHCA etiology

In this cohort, 64.8% (n=46) of patients were admitted with CA of a cardiac etiology, while 23.9% (n=17) of OHCA occurred because of respiratory pathology. The remaining 11.2% (n=8) patients experienced OHCA due to other underlying causes including cerebral hemorrhage (n=1), intoxication (n=1) and electrolyte disturbance (n=1). In 7.0% (n=5) patients, the etiology of OHCA remained unidentified. Serum GAL3 levels did not differentiate between patients with OHCA of cardiac etiology and those with a non-cardiac cause (day 0: p=0.976; day 2: p=0.979; Table I).

Serum GAL3 levels and myocardial dysfunction after OHCA

TTE performed upon admission revealed a reduced median LVEF of 35% (IQR 25-50%). GAL3 levels on day 0 or day 2 were unable to differentiate between patients with severely reduced LVEF ≤30% and those with LVEF >30% (day 0: p=0.784; day 2: p=0.994; Table I). There was no significant correlation of GAL3 and NT-proBNP (day 0: r=-0.147, p=0.261; day 2: r=0.084, p=0.710).

Serum GAL3 levels and neurological outcome after OHCA

In this cohort, 28.2% (n=20) of patients had favorable neurological outcome at hospital discharge (CPC 1-2). GAL3 was not associated with neurological outcome (day 0: p=0.098; day 2: p=0.325; Table I, Additional file 5).

GAL3 showed no correlation to NSE 48 h after ROSC (day 0: r=0.138, p=0.365; day 2: r=-0.015, p=0.929; Additional file 4). This lack of correlation persisted even after excluding patients treated with ECLS, which can cause hemolysis and potentially lead to falsely elevated NSE levels (day 0: r=0.267, p=0.098; day 2: r=0.058, p=0.729; Additional file 4). GAL3 levels were not significantly different between patients with low levels of NSE 48 h after ROSC and patients that reached the prognostic NSE threshold of 60 ng/ml (day 0: p=0.590; day 2: p=0.937). This result continued to hold true after excluding patients treated with ECLS (day 0: p=0.105; day 2: p=0.978, Table I).

Table I Further associations between serum GAL3 levels and parameters of PCAS

	GAL3 [ng/ml], median (IQR)	
	day 0	day 2
Etiology		
Cardiac (n=46)	38.92 (23.91-50.75)	12.63 (8.01-16.58)
Non-cardiac (n=20)	41.66 (26.06-52.90)	10.02 (4.24-21.44)
*p**	0.976	0.979
LVEF		
LVEF ≤30% (n=21)	37.58 (23.83-55.74)	13.35 (9.43-17.31)
LVEF >30% (n=36)	41.52 (24.79-50.51)	11.89 (7.58-21.57)
*p**	0.784	0.994
CPC		
1-2 (n=20)	28.63 (16.04-46.73)	10.09 (6.89-15.63)
3-5 (n=44)	41.52 (27.47-51.40)	14.44 (8.84-21.28)
*p**	0.098	0.325
NSE 48 h**		
≤60 ng/ml (n=21)	26.71 (17.28-42.70)	10.61 (7.61-16.65)
>60 ng/ml (n=21)	41.49 (28.63-53.22)	13.35 (5.21-21.35)
*p**	0.590	0.937

* The presented p-values are results of post-hoc multiple comparison tests on linear mixed models. Šidák's test was used to control for multiple testing. ** ECLS patients were excluded from this analysis. p<0.05 was considered significant. *CPC* cerebral performance category, *GAL3* galectin-3, *IQR* interquartile range, *LVEF* left-ventricular ejection fraction, *NSE* neuron-specific enolase, *PCAS* post-cardiac arrest syndrome.

Discussion

This study presents novel findings on the time course of serum GAL3 levels and its diagnostic and prognostic value after initial OHCA survival. Key observations include: First, serum GAL3 levels on hospital admission after OHCA were significantly higher than on day 2 and higher than levels observed in CAD controls (Figure 1). Second, elevated serum GAL3 levels on hospital admission are an independent predictor of in-hospital mortality after successful resuscitation of OHCA patients (Figure 2). Third, while no correlation was identified between GAL3 serum levels and NSE 48 h after ROSC or neurological outcome (CPC) at hospital discharge (Table I), GAL3 levels at admission are elevated in OHCA patients with cerebral edema on cCT (Table 3). Fourth, higher GAL3 levels on admission are associated with hypoperfusion and post-cardiac arrest shock reflected by prolonged need of vasopressor/inotropic support and inadequate lactate clearance (Table 3). However, no association was observed between GAL3 and cardiac etiology of OHCA, NT-proBNP levels or left-ventricular myocardial dysfunction (Table I). Fifth, GAL3 on admission correlates with IL-6 on admission, an independent predictor of mortality and PCAS severity [51-53].

Regulation

Upregulation of GAL3 has been observed in a variety of critically-ill patients in the intensive care unit (ICU) presenting with sepsis, trauma or COVID-19 [54-56]. In addition, elevation of GAL3 was reported in patients with severe heart failure with need for mechanical circulatory support and acute myocardial infarction (AMI) with hemodynamic instability [57, 58]. Two studies have previously revealed GAL3 elevation on hospital admission in serum of OHCA patients [43, 44]. The present study is the first to analyze the temporal profile of GAL3 in the early post-resuscitation period (Figure 1). GAL3 levels peaked on admission after OHCA and declined on day 2 to levels comparable to those observed in CAD controls suggesting that whole-body I/R injury is tied to GAL3 regulation. This finding is in accordance with elevated GAL3 levels in the context of I/R injury in patients with acute stroke who underwent endovascular therapy [59]. GAL3 levels were highest during cerebral ischemia and declined on day 1 and 3 after interventional reperfusion [59]. Additional data regarding the regulation of GAL3 in I/R is available in ST-elevation myocardial infarction (STEMI) patients [46]. Serum GAL3 levels were highest during myocardial ischemia and declined after reperfusion following PCI [60]. Patients with cardiogenic shock showed initial elevation and rapid downregulation of GAL3 24-72 h after establishing extracorporeal membrane oxygenation (ECMO) treatment [61].

The observed patterns of GAL3 regulation in the context of stroke, STEMI and shock are replicated in the present OHCA cohort, thereby indicating that the GAL3 concentration

peak might be linked to ischemia during no-flow/low-flow time during resuscitation. The subsequent decrease in GAL3 likely reflects resolution of ischemic stress after reperfusion. To further support this hypothesis, higher GAL3 levels on day 2 were observed in patients with ongoing ischemia due to post-cardiac arrest shock, reflected by prolonged need for vasopressor/inotropic support and inadequate lactate clearance (Table 3) [36, 62, 63]. The cellular origin of serum GAL3 levels observed in OHCA patients remains to be elucidated. While GAL3 is expressed in a variety of cell types including epithelial and inflammatory cells, GAL3 expression has been detected in microglia and astrocytes in the context of ischemic brain tissue [64, 65]. This expression has been demonstrated to regulate microglia activation and proliferation, as well as the expression of various proinflammatory cytokines [64-66]. In ischemic myocardium, GAL3 upregulation has been noted especially in cardiomyocytes and endothelial cells as well as infiltrating macrophages [38, 67-70]. GAL3 modulates apoptosis of cardiomyocytes, leukocyte adhesion and angiogenesis and inflammatory cytokine release after cardiac I/R injury [38, 67-70].

In-hospital mortality

Overall outcome prediction remains a central challenge during the early post-resuscitation phase [22]. Two previous studies have suggested a possible prognostic role of admission GAL3 levels in OHCA [43, 44]. In one prospective multicenter study, serum GAL3 levels at hospital admission following OHCA were higher in non-survivors and concentrations >26.6 ng/ml were identified as an independent risk factor for all-cause mortality after 4 weeks as well as 5 months of follow-up after initially survived OHCA [43]. A recent study has indicated that elevated GAL3 levels (>26.3 ng/ml) at the time of admission can serve as a predictor of mortality after 5.7 years in OHCA survivors [44]. The present study identified an optimal cut-off value to predict in-hospital mortality of ≥37.48 ng/ml (Figure 2). Therefore, our results are in line with the available literature suggesting that GAL3 levels on admission serves as a potential biomarker that might contribute to prognostication after OHCA. The short-term prognostic value of GAL3 suggested by this study needs to be validated in larger patient cohorts that should include a variety of OHCA etiologies to identify specific pathologies associated with GAL3 regulation.

Hemodynamic instability

Post-resuscitation shock occurs in up to 60% of OHCA patients, contributes to multi-organ failure, poor prognosis and requires early and aggressive management [22, 26, 71, 72]. The complex pathophysiology of post-resuscitation shock includes vasoplegia and myocardial dysfunction due to systemic I/R injury as well as sepsis-like syndrome

[1, 22]. In this cohort, GAL3 levels remained higher in patients with prolonged vasopressor requirements and inadequate lactate clearance on day 2 after ROSC (Table 3). This identifies GAL3 as a novel potential marker of prolonged hypoperfusion and shock after CA. Supporting these findings, GAL3 concentrations were observed to correlate with need for inotropic medication in acute heart failure, AMI and a cohort of patients after left-ventricular assist device implantation [58, 73, 74].

In the present cohort, GAL3 levels were unable to differentiate between patients with severe myocardial dysfunction and OHCA survivors with LVEF >30% (Table I). Additionally, there was no correlation between GAL3 levels and NT-proBNP (Table I). Evidence regarding the association between GAL3 levels and LVEF in other patient cohorts of acute cardiac dysfunction is available.

In a cohort of patients with AMI and left-ventricular (LV) dysfunction, baseline GAL3 measured within 46 h of presentation did not correlate with any LV parameters at baseline including LVEF [75]. Similarly, in STEMI patients treated with primary PCI, GAL3 levels did not show a relationship with LV volumes or LVEF during the acute phase of myocardial infarction (MI) or at one-year follow-up [76, 77]. In contrast to these reports, other studies observed higher baseline GAL3 concentrations in patients with lower LVEF in acute coronary syndrome (ACS) patients in general and STEMI patients specifically [58, 78]. Additionally, negative correlations of baseline GAL3 levels with LVEF at 4- and 6-month follow-up were shown in AMI patients [75, 79]. GAL3 on day 30 could predict left-ventricular remodeling which was associated with lower LVEF at 6 months after AMI [80]. In a population-based MI incidence cohort, heart failure development with reduced ejection fraction within 5 years was associated with baseline GAL3 elevation [81]. GAL3 was similarly associated with heart failure development in ACS patients in general and STEMI patients specifically [82, 83]. Overall, GAL3 does not show consistent associations to baseline LV-dysfunction in acute settings but the available clinical evidence reflects its role in promoting cardiac fibrosis and inflammation during post-infarction remodeling [75, 79, 80, 84].

Studies in AMI patients report that GAL3 and NT-proBNP were correlated moderately but GAL3 seemed more closely related to cardiac remodeling while NT-proBNP better reflected wall stress and hemodynamic changes [76, 85-87]. However, their prognostic utilities were complementary. In ACS and MI cohorts, combined biomarker models showed better risk prediction for mortality and adverse cardiovascular events [81, 83].

In recent years, evidence on lactate clearance as a surrogate parameter for resolution of hypoperfusion and shock has emerged [36]. Interpretation of a singular lactate value is difficult as lactate levels are representative of both lactate build-up due to e.g. tissue hypoxia during OHCA but are also influenced by post-CA aspects including persistent hemodynamic instability with hypoperfusion, systemic inflammatory reactions and

subsequent complications of PCAS that hinder lactate elimination processes [36, 62, 63]. Short-term lactate clearance within 3 h after admission was identified as a predictor of short-term survival at 72 h after ROSC [88]. Survivors to hospital discharge showed significantly greater lactate clearance within the first 6-12 h after admission than non-survivors [62, 89]. Greater lactate clearance within 6 h after ROSC predicted 30-day survival [90]. In OHCA patients without ROSC with need for ECLS, greater lactate clearance during the first 6 h after implementation of ECLS was associated with higher 30-day survival rates [63]. In line with these reports, this study shows that adequate lactate clearance is associated with survival to hospital discharge and GAL3 levels are higher in patients with inadequate lactate clearance (Table 3).

Neurological outcome

HIE accounts for the majority of fatalities after OHCA [1, 71]. After initial stabilization of an OHCA patient, a multimodal algorithm to evaluate the extent of HIE and to guide WLST decision-making is recommended by the ERC guidelines [22]. In the present study, GAL3 on admission demonstrated neither an association with NSE after 48 h, nor was there a correlation with neurological outcome as determined by CPC at the time of hospital discharge (Table I, Additional file 4 and 5). However, serum GAL3 levels were found to correlate with the presence of cerebral edema as depicted on cCT (Table 3). A recent analysis has identified GAL3 on admission as a predictor of long-term cerebral disability assessed by CPC at 5.7 years after OHCA [44].

Data on the prognostic value of GAL3 in ischemic brain damage is available from patients with stroke. GAL3 has been proposed as a valuable biomarker for the diagnosis of ischemic stroke in patients without features of stroke on cCT as it showed upregulation in response to ischemia of the brain [37]. Elevated serum GAL3 levels after acute ischemic stroke were associated with greater stroke severity, larger infarct volume and worse functional outcomes as well as mortality [91, 92].

Following ischemic brain injury in rat models, upregulated GAL3 expression was noted in neurons, activated microglia and astrocytes as well as proliferating endothelial cells and infiltrating macrophages [64, 93-95]. This upregulation peaked within days and persisted for weeks to months post-injury [94]. GAL3 was found to have neuroprotective effects by modulating tissue remodeling including angio- and neurogenesis [94]. Favorable effects of GAL3 on lesion size and neuronal apoptosis were described [64]. These effects are attributed to its interaction with insulin-like growth factor-1 (IGF-1) which modulates microglia proliferation [64].

GAL3 is closely involved in the regulation of blood-brain barrier (BBB) integrity following cerebral ischemia and hemorrhage. In a murine model of brain hemorrhage, GAL3 upregulation in brain capillary endothelial cells after injury contributed to BBB disruption

via loss of tight junction proteins [96]. Furthermore, GAL3 interacted with toll-like receptor 4 (TLR4), amplifying neuroinflammatory cascades that exacerbated BBB permeability [96, 97]. In murine models of subarachnoid hemorrhage, inhibition of GAL3 was found to attenuate BBB disruption, reduce brain edema and improve neurological outcomes [96]. Direct intracerebral application of GAL3 in rat models lead to reduced infarct volumes and improved functional outcome via increased vessel density and reduced neuronal apoptosis [97-99]. Mechanistically, GAL3 administration shifted microglial polarization toward anti-inflammatory phenotypes and downregulated pro-inflammatory cytokines [97, 98]. It caused upregulation of tight-junction proteins involved in BBB maintenance [98]. GAL3 also enhanced angiogenesis and neural progenitor proliferation, supporting tissue remodeling and functional recovery [94, 98, 99].·

Inflammation

The early post-resuscitation phase involves a systemic inflammatory response with elevated levels of a variety of cytokines such as IL-6 and TNF-α [11, 100, 101]. In this cohort, IL-6 increased on day 2 which is in line with other studies that show peak concentrations on day 2 after OHCA [51, 53]. IL-6 dysregulation during the early post-resuscitation phase has been identified as a surrogate parameter for organ dysfunction and PCAS severity and a predictor of ICU- and 30-day mortality [51-53, 102]. IL-6 elevation was also implicated in endothelial activation and injury resulting in hemodynamic instability with need for vasopressor support following OHCA [103, 104]. IL-6 induction in inflamed tissues occurs in response to pathogen and damage associated molecular patterns, both of which activate TLR and trigger – among others - nuclear factor kappa-beta (NF-kB) associated pathways of IL-6 messenger ribonucleic acid (mRNA) transcription [105]. A potential link between IL-6 and GAL3 exists via the activation of TLR4 by GAL3 [106]. In this study, admission GAL3 correlated with IL-6 on day 0, supporting its role in triggering inflammation via innate immune activation [40, 107, 108].

Apart from cytokine modulation, GAL3 has been found to influence key processes of inflammation after ischemic injury. GAL3 enhanced neutrophil function and macrophage recruitment and their polarization after ischemic injury [40, 68, 107]. Moreover, it supported fibroblast activation and collagen synthesis causing tissue remodeling, e.g. in the heart [38, 68]. These observations, in line with previous studies, suggest a possible involvement of GAL3 in the inflammatory response following CA.

Therapeutic targeting of GAL3 after ischemic injury in preclinical models has shown promising results including reduced inflammation and improved functional recovery [70]. In a rodent model of myocardial infarction, administration of GAL3 inhibitors significantly reduced cardiac fibrosis, attenuated ventricular remodeling and improved LVEF and

hemodynamics [109, 110]. Taken together, these results suggest GAL3 as a promising target for modulating the inflammatory response of I/R-injury which may have potential therapeutic implications after OHCA.

Limitations

Despite the prospective, two-center study design, the present study has several limitations and the results should be applied carefully to other situations and populations. Due to early mortality, not all outcome measures could be assessed in the entire cohort (n = 71). Specifically, brain edema was evaluated in 60 patients, CPC in 64 patients, NSE in 42 patients, lactate clearance in 55 patients and both LVEF and the need for prolonged vasopressor or inotropic support were assessed in 53 patients (Additional file 4). These missing data may introduce selection bias and should be considered when interpreting the subgroup results. The proportion of survivors (39%) in this study is considerably higher than reported in international studies and the German resuscitation register with survival rates below 35% [2-4]. The rather low mortality can be attributed, at least in part, to the high percentage of patients with shockable rhythms (52.1%) and cardiac cause (64.8%) as a trigger for CA which is known to be associated with better outcome [4]. Several patients died after life-sustaining therapy was withdrawn for poor neurological prognosis after neuroprognostication in line with ERC guidelines [22]. These patients cannot be differentiated from cases that fulfilled brain death criteria.

As is inherent to any observational study, we cannot prove a causal relationship but only describe the association between GAL3 and outcome measures. It cannot be excluded that, at least in some of the patients, GAL3 levels were already elevated before OHCA due to pre-existing comorbidities. In this cohort, subgroup analyses show that admission GAL3 levels are higher in non-survivors with prior ischemic heart disease, arterial hypertension and diabetes mellitus (Supplement II). However, the respective number of patients analyzed in each subgroup was small, hence, these results should be re-evaluated in larger patient settings. At the time of patient inclusion, targeted temperature management (TTM) at 32-36°C for 24 h was recommended in patients who remained unresponsive after ROSC [25]. Most of the resuscitated patients were undergoing TTM. We cannot exclude possible effects of TTM on GAL3 levels.

Conclusion and outlook

The present study demonstrates upregulation of GAL3 in the post-resuscitation period. GAL3 levels on admission are a possible predictor of in-hospital mortality after OHCA and are associated with cerebral edema and IL-6-driven inflammation. Moreover, elevated GAL3 levels were associated with ongoing post-cardiac arrest shock.

This was a hypothesis-generating study. Further examination is warranted based on our results and the available literature, particularly focusing on the relationship between GAL3 and I/R-injury of the brain as well as clinical neurological outcome. Regarding the pathophysiology of HIE, the origin of GAL3 in the hypoxic brain and its regulation patterns in a variety of cell types including astrocytes, glial cells, endothelial cells and neurons require clarification. Building on these results, more insight into the role of GAL3 in microglial activation, neuroinflammation, apoptosis and its involvement in BBB disruption of the hypoxic brain can be obtained. Future studies could include serial measurements of GAL3 in serum and cerebrospinal fluid to correlate with results of neuroimaging and biomarkers of BBB integrity. Animal models of HIE and CA might elucidate the therapeutic implications of GAL3 inhibition or augmentation for neurological outcome.

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Appendix

Supplementary material

Supplement I Cerebral Performance Categories

Category	Description	Characteristics
1. Good cerebral performance	normal life	- conscious - able to work and lead a normal life - minor psychological or neurologic deficits
2. Moderate cerebral disability	disabled but independent	- conscious - part-time work in sheltered environment - independent activities of daily life - hemiplegia, seizures, ataxia, dysarthria, dysphasia, permanent memory changes
3. Severe cerebral disability	conscious but disabled and dependent	- conscious - dependent on others for daily support - limited cognition
4. Coma/ Vegetative state	unconscious	- unconscious - no cognition - no verbal or psychologic interaction with environment
5. Brain death	certified brain dead or dead by traditional criteria	

Adapted from: The Brain Resuscitation Clinical Trial II Study Group. A randomized clinical trial of calcium entry blocker administration to comatose survivors of cardiac arrest. Design, methods, and patient characteristics. Control Clin Trials. 1991;12(4):525-45.

Supplement II GAL3 levels and prior disease

	GAL3 [ng/ml], median (IQR)	
	day 0	day 2
Arterial hypertension		
survivors (n=13)	20.63 (14.80-30.27)	45.55 (31.58-65.62)
non-survivors (n=25)	9.03 (4.24-14.81)	14.07 (10.29-21.32)
*p**	**<0.001**	0.304
Diabetes mellitus		
survivors (n=3)	12.80 (10.10-24.52)	6.88 (4.24-10.02)
non-survivors (n=8)	47.88 (38.57-73.61)	19.32 (16.84-21.39)
*p**	**0.006**	0.411
Ischemic heart disease**		
survivors (n=17)	26.58 (14.82-46.15)	10.32 (7.02-15.59)
non-survivors (n=16)	51.30 (31.66-80.12)	16.49 (13.31-19.16)
*p**	**0.013**	0.507

* The presented p-values are results of post-hoc multiple comparison tests on linear mixed models. Šidák's test was used to control for multiple testing. ** Defined as known coronary artery disease or prior myocardial infarction. p<0.05 was considered significant. *GAL3* galectin-3, *IQR* interquartile range.

List of abbreviations

ACS ..... acute coronary syndrome
AIDS ..... acquired immune deficiency syndrome
AMI ..... acute myocardial infarction
ATP ..... adenosine triphosphate
AUC ..... area under curve
BBB ..... blood-brain barrier
CA ..... cardiac arrest
CAD ..... coronary artery disease
cCT ..... cranial computed tomography
Chi^2 ..... chi-square
CI ..... confidence interval
cMRI ..... cranial magnetic resonance imaging
COPD ..... chronic obstructive pulmonary disease
COVID-19 ..... coronavirus disease 2019
CPC ..... Cerebral Performance Category
CPR ..... cardiopulmonary resuscitation
CVP ..... central venous pressure
DNA ..... deoxyribonucleic acid
e.g. ..... exempli gratia
ECG ..... electrocardiogram
ECLS ..... extra-corporeal life support
ECMO ..... extra-corporeal membrane oxygenation
EEG ..... electroencephalogram
ELISA ..... enzyme-linked immunosorbent assay
ERC ..... European Resuscitation Council
GAL3 ..... galectin-3
h ..... hours
HF ..... heart failure
HFpEF ..... heart failure with preserved ejection fraction
HIE ..... hypoxic-ischemic encephalopathy
HIV ..... human immunodeficiency virus
i.e ..... id est (that is)
I/R ..... ischemia/reperfusion
ICU ..... intensive care unit
IGF-1 ..... insulin-like growth factor-1
IL ..... interleukin
IQR ..... interquartile range

KHK ..... koronare Herzkrankheit
LV .....left-ventricular
LVEF ..... left-ventricular ejection fraction
MI .....myocardial infarction
min ……..... minutes
mRNA …… messenger ribonucleic acid
NF-kB …….... nuclear factor kappa-beta
NSE .....neuron-specific enolase
NT-proBNP ..... n-terminal pro brain natriuretic peptide
OHCA ..... out-of-hospital cardiac arrest
OR ..... odds ratio
PCAMD.....post-cardiac arrest myocardial dysfunction
PCAS..... post-cardiac arrest syndrome
PCI .....percutaneous coronary intervention
r .....rho
ROC ..... receiver operating characteristics
ROS..... reactive oxygen species
ROSC .....return of spontaneous circulation
STEMI .....ST-elevation myocardial infarction
TLR.....toll-like receptor
TNF .....tumor necrosis factor
TTE.....transthoracic echocardiography
TTM ..... targeted temperature management
USA .....United States of America
WLST .....withdrawal of life-sustaining treatment
YI ……..Youden Index

Contribution of the doctoral candidate to the original publication

I hereby confirm that I, Swantje Nickelsen, contributed in several key areas to the publication:

Nickelsen S, Darrelmann EG, Seidlmayer L, Fink K, Britsch S, Duerschmied D, et al. Galectin-3 as a marker to characterize post-cardiac arrest syndrome in initially survived out-of-hospital cardiac arrest: a prospective two-center study. Resusc Plus. 2025;25:101048.

The project's general conceptualization was undertaken by T. Helbing, A. Elsässer and K. Fink. T. Helbing and I then developed the specific research questions for this publication. I contributed to the acquisition of funding from the University Oldenburg's "Forschungspool"- a task that the project's administrator T. Helbing was mainly responsible for. I recruited patients for the study center Oldenburg and collected necessary data together with E. Grosse Darrelmann and L. Seidlmayer. Both aforementioned co-authors provided valuable resources for patient follow-up and data collection. With the support of G. Theilmeier and his team, I performed GAL3 ELISA measurements for the samples obtained at the study center in Oldenburg. The data obtained at the University Hospital Freiburg was provided by T. Helbing, K. Fink and D. Dürschmied. I was responsible for data curation and formal statistical analysis. Together with A. Elsässer and T. Helbing, I produced the necessary visualizations. Finally, T. Helbing and I developed the original draft of the manuscript. I was then able to revise and edit the manuscript thanks to the valuable input provided by all co-authors. The whole project and development of the original publication were supervised by S. Britsch, D. Dürschmied and R. Scharf.

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Erklärungen

Ich, Swantje Nickelsen, erkläre an Eides statt, dass ich diese Dissertation selbständig und ohne fremde unzulässige Hilfe erbracht habe. Das heißt, dass ich die Dissertation ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt und die aus fremden Quellen direkt oder indirekt übernommenen Gedanken als solche kenntlich gemacht habe.

Ich erkläre darüber hinaus, dass der Inhalt der Dissertation nicht schon überwiegend für eine eigene Bachelor-, Master-, Diplom- oder ähnliche Prüfungsleistung verwendet wurde.

Hannover, 22.10.2025 _[redacted]