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Predicting long-term outcomes after cardiac arrest by using serum neutrophil gelatinase-associated lipocalin

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ABSTRACT

Objectives: Neutrophil gelatinase-associated lipocalin (NGAL) is secreted by various tissues in pathologic states. Previous studies reported that post-cardiac arrest serum NGAL levels correlate with short-term neurologic outcomes and survival. The aim of this study was to examine the associations between NGAL levels post-cardiac arrest and long-term outcomes and survival.

Methods: This prospective observational study and retrospective review included adult out-of-hospital cardiac arrest survivors who were treated by hypothermia-targeted temperature management. Serum NGAL was assessed at 0, 24, 48, and 72 h after return of spontaneous circulation. The primary outcome was poor outcome at six months after cardiac arrest, defined as cerebral performance category score of 3–5. The secondary outcome was six-month mortality.

Results: In total, 76 patients were analyzed. The patients with poor outcomes showed significantly higher NGAL levels at 24, 48 and 72 h after cardiac arrest than the patients with good outcomes. Long-term survival rates were significantly lower in the high-NGAL group than in the low-NGAL group at each time point. Subgroup analysis of patients who survived 72 h showed that only serum NGAL 72 h after cardiac arrest had prognostic value for long-term outcomes (area under the receiver operating characteristic curve = 0.72; $p = 0.02$).

Conclusions: Post-cardiac arrest serum NGAL is associated with long-term outcomes and survival; particularly, three days post-cardiac arrest is the optimal time point for predicting long-term outcomes. However, the predictive power of NGAL is unsatisfactory, and it should be regarded as an additional prognostic modality.

1. Introduction

Predicting the neurologic outcomes of post-cardiac arrest syndrome (PCAS) patients is challenging, especially in patients who receive sedative drugs or neuromuscular blocking agents during hypothermia-targeted temperature management (TTM). No single early-diagnostic test is regarded as a prognostic gold standard, and therefore, multimodal prognostication is currently recommended [1,2]. Serum biomarkers are ideal for the prognostication of patients undergoing hypothermia-TTM because they are easy to obtain and are not affected by sedative drugs. However, the predictive power of brain-specific biomarkers such as neuron-specific enolase (NSE) and S100B is not satisfactory [3]. Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the lipocalin superfamily, known as a biomarker of acute kidney injury (AKI) [4,5]. Recently, NGAL has been suggested as a potential predictor of post-cardiac arrest outcomes [6-9]. However, NGAL is not brain-specific. In addition to kidney epithelial cells, NGAL is secreted by various tissues including lung and liver in various pathologic states [10,11]. Thus, NGAL may not correlate with actual neuro-cognitive long-term outcomes. The purpose of this study was to determine whether serum NGAL is a potentially adjunctive biomarker of long-term outcomes and survival after cardiac arrest. In addition, we intended to identify the relationship between outcomes and NGAL levels over time and to elucidate the sampling time points that showed the best discriminating power.

Abbreviations: PCAS, post-cardiac arrest syndrome; TTM, targeted temperature management; NSE, neuron-specific enolase; NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; CPC, cerebral performance category; CT, computed tomography; DWI, diffusion-weighted magnetic resonance imaging; SEP, somatosensory evoked potential; AUROC, area under the receiver operating characteristic curve; CKD, chronic kidney disease.

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Table 1
Patient characteristics.

Characteristic	Poor outcome (n = 81)	Good outcome (n = 35)	p
Age	58.20 ± 14.84	50.11 ± 15.17	0.01
Male	55 (67.9)	26 (74.3)	0.49
Previous medical history			
Myocardial infarction	3 (5.1)	0 (0)	1
Congestive heart failure	4 (6.8)	1 (5.9)	1
Peripheral vascular disease	0 (0)	0 (0)	
Cerebrovascular disease	4 (6.8)	0 (0)	0.57
COPD	3 (5.1)	0 (0)	1
Connective tissue disease	1 (1.7)	0 (0)	1
Peptic ulcer disease	1 (1.7)	0 (0)	1
Mild liver disease[a]	0 (0)	0 (0)	
Moderate-severe liver disease[b]	0 (0)	0 (0)	
Diabetes with organ damage	5 (8.5)	3 (17.6)	0.37
Hemiplegia	0 (0)	0 (0)	
Moderate-severe renal disease[c]	4 (6.8)	3 (17.6)	0.18
Any tumor (within last 5 years)	1 (1.7)	0 (0)	1
Lymphoma	0 (0)	0 (0)	
Leukemia	0 (0)	0 (0)	
Metastatic solid tumor	0 (0)	0 (0)	
AIDS	0 (0)	0 (0)	
Pancreatitis	0(0)	0 (0)	
Alcohol abuse	5 (9.3)	0 (0)	0.58
Homeless	0 (0)	0 (0)	
Witness			0.07
Yes	51 (62.9)	28 (80.0)	
No	30 (37.1)	7 (20.0)	
Bystander CPR			0.35
Yes	41 (51.6)	21 (60.0)	
No	40 (49.4)	14 (40.0)	
Initial cardiac arrest rhythm			<0.01
Non-shockable	73 (90.1)	8 (22.9)	
Shockable	8 (9.9)	27 (77.1)	
Anoxic time (min)	32 [18–44]	19 [11–29]	<0.01
Cause of cardiac arrest			<0.01
Cardiac	23 (28.4)	31 (88.6)	
Non-cardiac	58 (71.6)	4 (11.4)	

Abbreviations: COPD, chronic obstructive pulmonary disease; AIDS, acquired immunodeficiency syndrome; CPR, cardiopulmonary resuscitation.
Data are presented as n (%), means ± standard deviations or medians with interquartile ranges, as appropriate.
[a] Cirrhosis without portal hypertension or chronic hepatitis.
[b] Moderate: cirrhosis with portal hypertension without bleeding, severe: cirrhosis with portal hypertension with bleeding.
[c] Moderate: creatinine ≥ 3 mg/dL, severe: dialysis; uremia; kidney transplantation.

2. Methods

2.1. Study design and setting

This was a prospective, observational study and retrospective review of consecutive patients, conducted at a university-affiliated hospital providing hypothermia-TTM to over 45 patients annually. Our Institutional review board approved this study (UC17RESI0058). The board waived the consent form requirement.

2.2. Population

From March 2013 to December 2014, all patients who had undergone hypothermia-TTM were included. Adults (≥18 years old) who had survived out-of-hospital cardiac arrest (OHCA) and maintained return of spontaneous circulation (ROSC) longer than 20 min were eligible for the hypothermia-TTM. Contraindications for hypothermia-TTM were regain of consciousness after ROSC, cerebral hemorrhage, suspected or confirmed hemorrhagic shock, terminal illness, or low baseline cognitive/neurologic functions as measured by cerebral performance category (CPC) 3 or 4.

2.3. TTM protocol

After ruling out cerebral hemorrhage by brain computed tomography (CT), we maintained TTM using an automatic surface cooling device using gel pads; the target temperature was 33 °C for 24 h, followed by 12 h of re-warming at the rate of 0.25 °C per hour. Sedative and paralytic agents were continuously administered to control shivering during the hypothermic period. Once the temperature reached 36.8 °C, we continued normothermia-TTM for an additional 36 h.

2.4. Measurements

We recorded baseline clinical data such as age, sex, previous medical history, cause of cardiac arrest, cardiac arrest rhythm, presence of witness, bystander cardiopulmonary resuscitation, anoxic time, and development of AKI within 72 h according to the AKI Network definition as one of the following: an increase in serum creatinine of ≥0.3 mg/dL within 48 h, an increase in serum creatinine to ≥1.5 times baseline within the previous seven days (if available), or urine volume ≤ 0.5 mL/kg/h for 6 h [12].

We assessed serum concentrations of NGAL 0, 24, 48 and 72 h after ROSC. We collected blood samples in tubes containing ethylenediaminetetraacetic acid and measured within 30 min with Triage NGAL fluorescence immunoassay (Alere Inc., Waltham, MA, USA), which has a measurable range of 15–1300 ng/mL. In the patients who survived

Table 2
Serum NGAL levels after cardiac arrest.

	Time	Good outcome (n = 17)	Poor outcome (n = 59)	p
Complete group (n = 76)	0 h NGAL, ng/mL (n = 74)	113 [82–442]	306 [145–558]	0.062
	24 h NGAL, ng/mL (n = 61)	157 [87–393]	438 [176–1070]	0.013
	48 h NGAL, ng/mL (n = 51)	146 [93–352]	412 [163–987]	0.049
	72 h NGAL, ng/mL (n = 47)	118 [64–427]	304 [148–1100]	0.017
	Time	Good outcome (n = 15)	Poor outcome (n = 31)	p
72-hour survivor subgroup without missing NGAL values (n = 46)	0 h NGAL, ng/mL (n = 46)	113 [82–442]	184 [112–404]	0.373
	24 h NGAL, ng/mL (n = 46)	157 [87–437]	314 [136–636]	0.108
	48 h NGAL, ng/mL (n = 46)	146 [93–352]	382 [163–987]	0.094
	72 h NGAL, ng/mL (n = 46)	118 [64–427]	310 [143–1150]	0.017

Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin.
Data are presented as medians with interquartile ranges.

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