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Predictive performance of plasma neutrophil gelatinase-associated lipocalin for neurologic outcomes in out-of-hospital cardiac arrest patients treated with targeted temperature management

A prospective observational study

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Abstract

Few studies have demonstrated the prognostic potential of neutrophil gelatinase-associated lipocalin (NGAL) in post-cardiac arrest patients. This study evaluated the usefulness of plasma NGAL in predicting neurologic outcome and mortality in out-of-hospital cardiac arrest (OHCA) patients treated with targeted temperature management (TTM). A prospective observational study was conducted between October 2013 and April 2016 at a single tertiary hospital. We enrolled 75 patients treated with TTM and collected their demographic data, cardiopulmonary resuscitation-related information, data on plasma NGAL concentration, and prognostic test results. Plasma NGAL was measured at 4 hours after return of spontaneous circulation (ROSC). The primary endpoint was the neurologic outcome at discharge and the secondary outcome was 28-day mortality. Neurologic outcomes were analyzed using a stepwise multivariate logistic regression while 28-day mortality was analyzed using a stepwise Cox regression. The predictive performance of plasma NGAL for neurologic outcome was measured by the area under the receiver operating characteristic curve and the predictability of 28-day mortality was measured using Harrell C-index. We also compared the predictive performance of plasma NGAL to that of other traditional prognostic modalities for outcome variables. Thirty patients (40%) had good neurologic outcomes and 53 (70.7%) survived for more than 28 days. Plasma NGAL in patients with good neurologic outcomes was 122.7 ± 146.7 ng/ml, which was significantly lower than that in the poor neurologic outcome group (307.5 ± 269.6 ng/ml; $P < .001$). The probability of a poor neurologic outcome was more than 3.3-fold in the NGAL >124.3 ng/ml group (odds ratio, 3.321; 95% confidence interval [CI], 1.265–8.721]). Plasma NGAL in the survived group was significantly lower than that in the non-survived group (172.7 ± 191.6 vs 379.9 ± 297.8 ng/ml; $P = .005$). Plasma NGAL was significantly correlated with 28-day mortality (hazard ratio 1.003, 95% CI 1.001–1.004; $P < .001$). The predictive performance of plasma NGAL was not inferior to that of other prognostic modalities except electroencephalography. Plasma NGAL is valuable for predicting the neurologic outcome and 28-day mortality of patients with OHCA at an early stage after ROSC.

This study was registered at ClinicalTrials.gov on November 19, 2013 (Identifier: NCT01987466).

Abbreviations: AKI = acute kidney injury, AUC = area under the receiver operating characteristic curve, CI = confidence interval, CPC = cerebral performance categories, CPR = cardiopulmonary resuscitation, EEG = electroencephalogram, ESRD = end-stage renal disease, HR = hazard ratio, IHCA = in-hospital cardiac arrest, MRI = magnetic resonance imaging, NGAL = neutrophil gelatinase-associated lipocalin, NSE = neuron-specific enolase, OHCA = out-of-hospital cardiac arrest, ROSC = return of spontaneous circulation, SD = standard deviation, SSEP = somatosensory-evoked potential, TTM = targeted temperature management.

Keywords: mortality, neurologic outcome, out-of-hospital cardiac arrest, plasma neutrophil gelatinase-associated lipocalin, targeted temperature management

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1. Introduction

As post-cardiac arrest interventions including targeted temperature management (TTM) have improved, currently existing prognostic modalities do not accurately reflect the prognosis of post-cardiac arrest patients. Previously, a patient's prognosis was presumed to be poor if myoclonic status epilepticus occurred on the first day of cardiac arrest or if serum neuron-specific enolase (NSE) levels exceeded 33 ng/ml.[1,2] However, in the era of TTM, patients with post-anoxic myoclonus can recover consciousness, and the false-positive rates of NSE are increasing when the traditional cut-off value is applied.[3–5] Therefore, the present guideline recommends that patient prognosis be assessed by combining several prognostic tests 4.5 to 5 days after the return of spontaneous circulation (ROSC).[6,7] However, this requires vast medical resources to determine the correct prognosis. Therefore, it has become increasingly necessary to develop alternative prognostic modalities that can be employed early after ROSC.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein distributed in the kidney, liver, and epithelial cells. NGAL is secreted from the damaged nephron upon kidney injury and can be detected in the urine and blood 2 hours post-injury. It is widely used for the early diagnosis of acute kidney injury (AKI),[8,9] and is also reported to be a prognostic factor in patients with cardiovascular disease, traumatic brain injury, and ischemic stroke.[10–12] Recently, a few studies have investigated NGAL expression in post-resuscitation syndrome patients. Park et al reported that high plasma NGAL levels were associated with the occurrence of AKI and poor neurological prognosis in out-of-hospital cardiac arrest (OHCA) patients.[13] Additionally, Elmer et al reported that lower plasma NGAL predicted survival-to-discharge in patients with post-resuscitation syndrome.[14] However, these studies did not consider whether they were OHCA or in-hospital cardiac arrest (IHCA) patients. Because the prognosis of OHCA and IHCA patients vary, it is reasonable to evaluate the prognostic performance of NGAL in these 2 groups separately. Hence, the aim of this study was to evaluate the usefulness of plasma NGAL in predicting neurological prognosis and mortality in adult OHCA patients treated with TTM. We also compared the predictive power of plasma NGAL levels to those of traditional prognostic tests such as NSE.

2. Materials and methods

2.1. Study design and participants

We performed a prospective, observational study to evaluate the ability of plasma NGAL to predict neurological prognosis and mortality in adult OHCA patients who underwent both successful cardiopulmonary resuscitation (CPR) in the emergency department and TTM between October 2013 and April 2016. According to the TTM protocol of our institution, the exclusion criteria were as follows:

- age <19 years,
- arrival at our hospital more than 4 hours after ROSC,
- hemorrhagic shock,
- cerebral hemorrhage,
- traumatic arrest,
- pre-existing coma or terminal illness, and
- refusal of caregivers for TTM.

We also excluded patients who were receiving renal replacement therapy, missed NGAL testing, died within 4 hours after ROSC, transferred to another hospital prior to completing TTM, or lacked their caregivers' consent to participate in this study.

2.2. Ethics

The study was reviewed and approved by the institutional review board of Yonsei University College of Medicine, Severance Hospital (Protocol number: 2013–0833-002, date of approval: September 24, 2013).

2.3. Study protocol

According to the TTM protocol of our hospital, the target temperature was set to below 36°C when the cause of arrest was presumed to be cardiogenic and to 32°C to 34°C when it was presumed to be non-cardiogenic. The Arctic Sun Temperature Management System™ (Medivance, Louisville, CO) was used for maintaining the core temperature. For non-cardiogenic arrests, 30 ml/kg of normal saline at 4°C was intravenously infused at 100 ml/minute within 3 hours of ROSC to decrease the patient's temperature. Baseline demographic data (age, sex, and underlying disease), CPR-related information (cause of arrest, witnessed/unwitnessed, bystander CPR status, total CPR time, total epinephrine dosage, and initial rhythm), target temperature for TTM, plasma NGAL concentration, and results of neurological prognosis prediction tests were collected. To predict the prognosis, the somatosensory-evoked potential (SSEP) was tested 24 to 72 hours after ROSC, and patients with bilateral absence of N20 were classified as non-responders. Electroencephalogram (EEG) was performed within 72 hours of commencing TTM. The EEG results were used to identify malignant patterns (status epilepticus, alpha coma, burst suppression, generalized suppression, and nonreactive EEG) vs benign patterns (all other results). The SSEP and EEG test results were interpreted by a board-certified neurologist. Brain magnetic resonance imaging (MRI) was performed 48 to 72 hours after ROSC and was interpreted by a board-certified radiologist. Patients were classified into 2 groups, hypoxic vs non-hypoxic injury, based on the diffusion-weighted image. The NSE was measured at 72 hours after ROSC. The primary endpoint of this study was the neurologic outcome at the time of discharge, while the secondary outcome was the 28-day mortality. Neurological outcomes were assessed using the cerebral performance categories (CPC) scale. We defined a good outcome as a CPC score of 1 or 2 and a poor outcome as a score of 3, 4, or 5.

2.4. Measurement of plasma NGAL

Based on a previous study, which revealed that plasma NGAL showed a significant change approximately 2 to 4 hours after kidney injury, the plasma NGAL was measured 4 hours after ROSC.[15]

Sixty cases were measured between October 2013 and September 2015 using the Alere Triage Meter Pro (Alere, Inc., San Diego, CA, USA), and 15 cases were measured between October 2015 and April 2016 using the Hitachi 7600 Automatic Analyzer (Hitachi Medical Corporation, Tokyo, Japan). To adjust for the different values obtained using the 2 devices, samples collected from 37 patients were tested simultaneously using both instruments, and the following formula based on the

Passing and Bablok regression[16] was used for data conversion: Y (Hitachi) = −38.29 + 0.9286× (Alere), (r = 0.870). The test results presented in this study are based on the Hitachi Medical Corporation as the standard, and the reference interval is 37 to 106 ng/ml.

2.5. Statistical analysis

Statistical analyses were conducted using SAS (version 9.2, SAS Inc, Cary, NC, USA). Between May 2012 and March 2013, 11 of 33 patients who were treated with TTM had good neurologic outcomes, based on which we calculated the sample size power. We assumed the predictive accuracy of NGAL to be 0.7, and we estimated that a sample size of 73 (24 and 49 patients with good and poor neurologic outcomes, respectively) would be sufficient to evaluate the primary endpoint at a significance level of 0.05 (2-sided) with 80% power.

The categorical variables are described as frequencies (%), while continuous variables are described as mean ± standard deviation (SD) or mean (95% confidence interval [CI]). The patients were divided into good or poor neurologic outcome groups as well as 28-days survival and non-survival groups. The independent t test was used for continuous variables while the Chi-Squared or Fisher exact test was used for categorical variables. Multivariate analysis was conducted using variables with P values <.05 on univariate analysis. Because cardiogenic arrest, shockable rhythm, and target temperature below 36°C were highly correlated with one another, shockable rhythm, and target temperature below 36°C were dropped from subsequent analysis. Neurologic outcomes were analyzed using a stepwise multivariate logistic regression while 28-day mortality was analyzed using a stepwise Cox regression. The predictive performance of plasma NGAL for neurologic outcome was measured by the area under the receiver operating characteristic curve (AUC); a cut-off value was chosen on the basis of the Youden index (defined as sensitivity + specificity − 1). Moreover, the predictability of 28-day mortality was measured using Harrell C-index. The cut-off value was determined using O'Quigley method with maximized log-rank test statistics; Kaplan–Meier survival curves for 28-day mortality were generated, and the log-rank test was applied using this cut-off value. To compare the predictive performance between NGAL and other prognostic tests, the bootstrapping method (1000 re-sampling trials) was used.[17]

3. Results

3.1. Study population

A total of 349 OHCA patients who underwent successful CPR were enrolled during the study period. We excluded 201 patients on the basis of the TTM protocol at our institution as well as another 73 on the basis of the aforementioned exclusion criteria. Ultimately, 75 patients were included in the study (Fig. 1); their mean age was 58.8 ± 17.1 years, and 53 (70.7%) were male. The patients' demographic and cardiac arrest-related data are summarized in Table 1.

3.2. Neurologic outcome

Thirty patients (40.0%) had good neurologic outcomes. The cardiogenic cause of arrest, initial shockable rhythm, target temperature was below 36°C, and shorter CPR time were significantly associated with good neurologic outcomes (Table 1). The mean value of plasma NGAL in patients with good neurologic outcomes was 122.7±146.7 ng/ml, which was significantly lower than that of patients with poor neurologic outcomes (307.5 ± 269.6 ng/ml; P < .001.) A stepwise multivariate analysis revealed that plasma NGAL and cardiogenic cause of arrest were independently associated with poor neurologic outcome (Table 2). The AUC of plasma NGAL was 0.733 (95% CI, 0.617–0.850); the sensitivity was 82.2% and the specificity was 60.0% when the cut-off value was set to 124.3 ng/dl. The probability of having a poor neurologic outcome was more than 3.3-fold in patients with NGAL levels of 124.3 ng/dl or more (odds ratio 3.321, 95% CI 1.265–8.721). When comparing AUCs, NGAL had a similar prognostic performance to NSE, SSEP, and brain MRI; only EEG was a more reliable predictor than plasma NGAL (P = .01) (Fig. 2A).

3.3. 28-day mortality

At 28 days, 53 patients (70.7%) had survived and 22 (29.3%) had died. The survived group comprised more patients whose cause of arrest was cardiogenic and whose initial ECG rhythm was shockable (Table 1). The mean value of plasma NGAL in the survived group was 172.7 ± 191.6 ng/ml, which was significantly lower than that in the non-survived group (379.9±297.8 ng/ml; P = .005). On a stepwise multivariate analysis (Table 2), plasma NGAL was significantly correlated with 28-day mortality (hazard ratio [HR] 1.003, 95% CI 1.001–1.004; P < .001). Moreover, when the cut-off value was set at >167.0 ng/dl, the 28-day mortality was increased by approximately 5.3-fold (HR 5.348, 95% CI 1.970–14.520; P = .001). Kaplan–Meier curves demonstrated a significantly increased 28-day mortality with this cut-off value (P < .001) (Fig. 3). Harrell C-index of plasma NGAL for predicting 28-day mortality was 0.720 (SD, 0.064), and there was no significant difference in prognostic performance for 28-day mortality among the examined prognostic factors (Fig. 2B).

4. Discussion

Our investigation revealed that plasma NGAL measured 4 hours after ROSC among adult OHCA patients who were treated with TTM was associated with both the neurologic outcome at the time of discharge as well as 28-day mortality. Specifically, the probability of poor neurologic outcome was 3.3-fold greater when plasma NGAL levels were 124.3 ng/dl or higher, while 28-day mortality was 5.3-fold greater when NGAL levels were above 167.0 ng/dl. Additionally, the predictive performance of plasma NGAL was not inferior to those of pre-existing prognostic factors other than EEG.

Post-resuscitation syndrome is defined as multi-organ dysfunction caused by systemic ischemia and reperfusion.[18] The brain is the organ most sensitive to ischemic injury; therefore, ischemia occurring in the less sensitive kidney indicates that brain ischemia very likely occurred beforehand. However, Yanta et al reported no correlation between renal dysfunction and survival discharge, although such dysfunction occurred at a high rate (37%).[19] A limitation of their study was that the authors defined renal dysfunction on the basis of classical indicators such as serum creatinine level and urine output and therefore did not assess the occurrence of subclinical AKI. Moreover, they included all types of AKI that occurred within 7 days after ROSC, and therefore

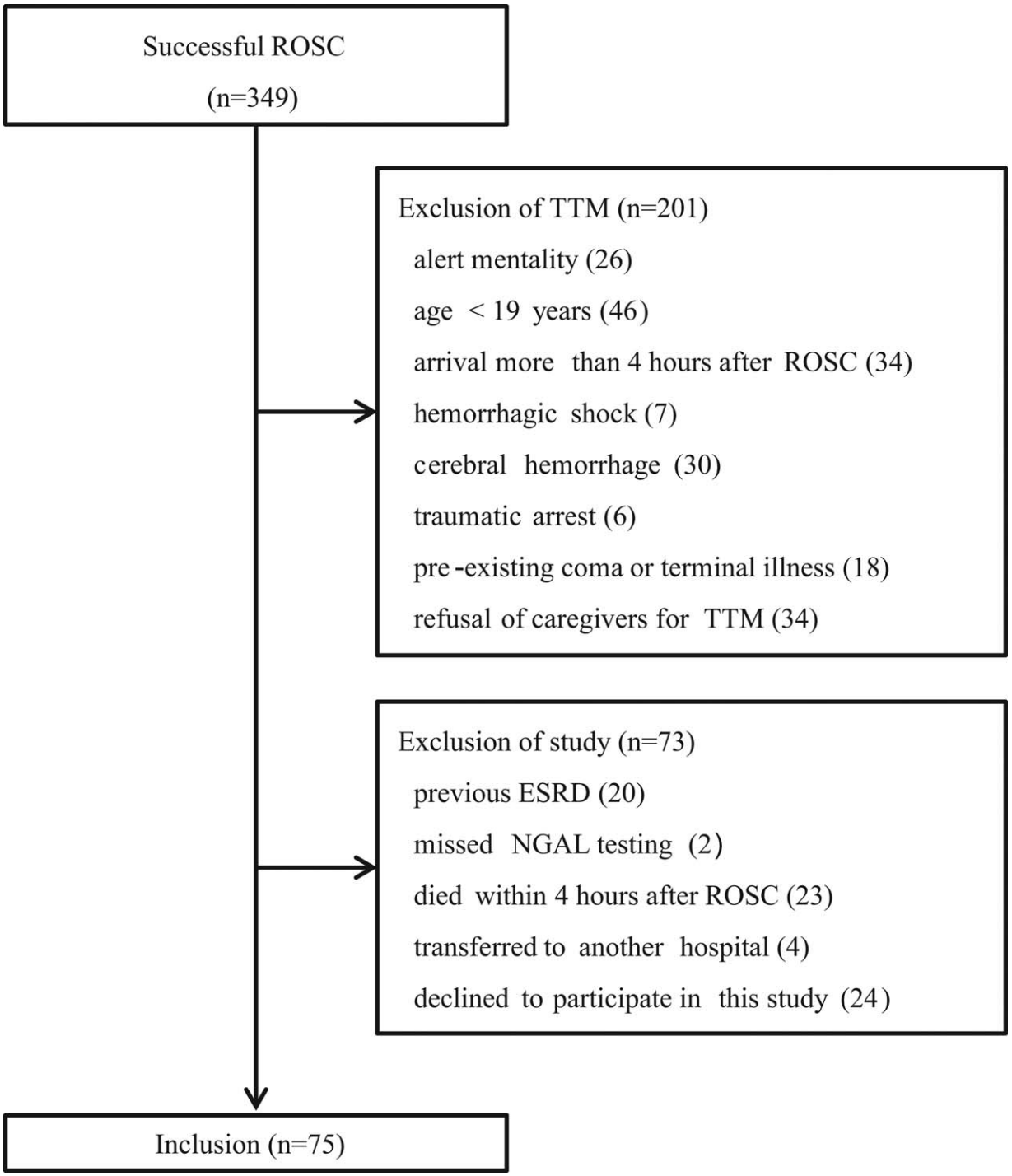

Figure 1. Flow diagram of the study participants. ROSC, return of spontaneous circulation; TTM, targeted temperature management; ESRD, end-stage renal disease; NGAL, neutrophil gelatinase-associated lipocalin.

could not distinguish between AKI resulting from cardiac arrest and that occurring after ROSC. However, NGAL levels from a single sample collected within a short time after ROSC could reflect not only AKI but subclinical renal ischemia; hence, AKI that occurred after ROSC could be excluded. Furthermore, a recent study found that NGAL may be directly expressed upon hypoxic damage to brain tissue and is associated with long-term and short-term mortality in patients with ischemic stroke.[10]

To date, few studies have investigated the association between NGAL and patient prognosis following post-cardiac arrest. Park et al reported that serum NGAL was significantly associated with the incidence of AKI, neurologic outcome, and 30-day survival in OHCA patients. In their study, the cut-off value for plasma NGAL, which was measured using an Alere instrument, was <129.5 ng/ml for good neurologic outcome and <153.5 ng/ml for 30-day survival.[13] Their cut-off value for good neurologic

Table 1

Baseline demographic data, CPR-related information, and results of prognostic tests of the study population.

Variable	Neurologic outcome			28-day mortality		
	Good (n = 30)	Poor (n = 45)	*P* value	Survival (n = 53)	Death (n = 22)	*P* value
Age (years)	55.9 ± 18.0	60.7 ± 16.5	.24	57.9 ± 16.9	60.8 ± 17.8	.52
Male sex, n (%)	22 (73.3)	31 (68.9)	.68	40 (75.5)	13 (59.1)	.16
Hypertension, n (%)	12 (40.0)	24 (53.3)	.26	25 (47.2)	11 (50)	.82
Congestive heart failure, n (%)	6 (20.0)	6 (13.3)	.53	10 (18.9)	2 (9.1)	.49
Cardiogenic arrest, n (%)	24 (80.0)	13 (28.9)	<.001	32 (60.4)	5 (22.7)	.003
Witnessed arrest, n (%)	25 (83.3)	31 (68.9)	.16	42 (79.3)	14 (63.6)	.16
Bystander CPR, n (%)	22 (73.3)	29 (64.4)	.42	36 (67.9)	15 (68.2)	.98
Shockable rhythm, n (%)	18 (60.0)	13 (28.9)	.007	26 (49.1)	5 (22.7)	.04
Total CPR time (min)	19.1 ± 14.8	29.6 ± 17.5	.008	23.3 ± 17.8	30.4 ± 14.6	.1
Total epinephrine dosage (mg)	1.8 ± 3.0	3.2 ± 2.6	.05	2.3 ± 2.9	3.3 ± 2.5	.17
Target temperature, n (%)			.004			.26
33°C	6 (20)	24 (53.3)		19 (35.9)	11 (50)	
<36°C	24 (80)	21 (46.7)		34 (64.2)	11 (50)	
NGAL (ng/ml)	122.7 ± 146.7	307.5 ± 269.6	<.001	172.8 ± 191.6	379.9 ± 297.8	.005
NSE (ng/ml) (n = 33)	32.0 ± 15.3	149.9 ± 129.2	<.001	84.9 ± 100.9	193.2 ± 137.9	.02
SSEP (n = 41), n (%)			<.001			.006
Responder	14 (93.3)	8 (30.8)		21 (65.6)	1 (11.1)	
Nonresponder	1 (6.7)	18 (69.2)		11 (34.4)	8 (88.9)	
EEG (n = 65), n (%)			<.001			<.001
Benign pattern	27 (96.4)	6 (16.2)		33 (66.0)	0 (0.0)	
Malignant pattern	1 (3.6)	31 (83.8)		17 (34.0)	15 (100.0)	
Brain MRI (n = 45), n (%)			<.001			.22
Positive for hypoxic damage	7 (30.4)	19 (86.4)		21 (53.9)	5 (83.3)	
Negative for hypoxic damage	16 (69.6)	3 (13.6)		18 (46.2)	1 (16.7)	

CPR = cardiopulmonary resuscitation, EEG = electroencephalogram, MRI = magnetic resonance imaging, NGAL = neutrophil gelatinase-associated lipocalin, NSE = neuron-specific enolase, SSEP = somatosensory evoked potential.

Table 2

Multivariate regression analysis for predicting poor neurologic outcomes and 28-day mortality.

Variable	Neurologic outcome		28-day mortality	
	OR	95% CI	HR	95% CI
Cardiogenic arrest	0.125	0.039–0.396	0.303	0.110–0.835
NGAL	1.004	1.001–1.007	1.003	1.001–1.004

CI = confidence interval, HR = hazard ratio, NGAL = neutrophil gelatinase-associated lipocalin, OR = odds ratio.

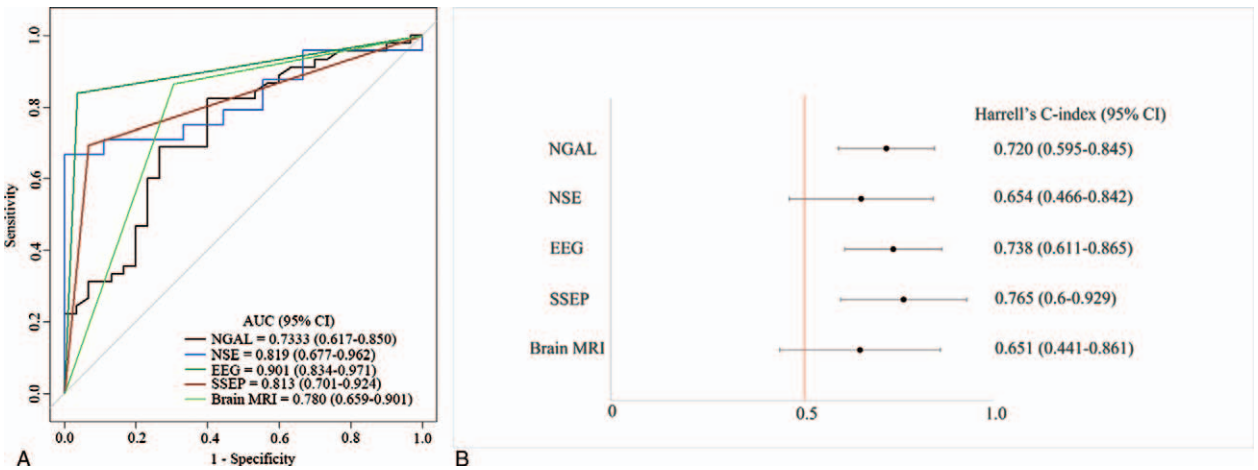

Figure 2. Predictive power of each prognostic test for neurologic outcomes and 28-day mortality. (A) Receiver operating characteristics curve for each prognostic factor to predict poor neurologic outcome. (B) Harrell C-index comparison for each prognostic factor to predict 28-day mortality: AUC, area under the curve; CI, confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; NSE, neuron specific enolase; EEG, electroencephalogram; SSEP, somatosensory evoked potential; MRI, magnetic resonance imaging.

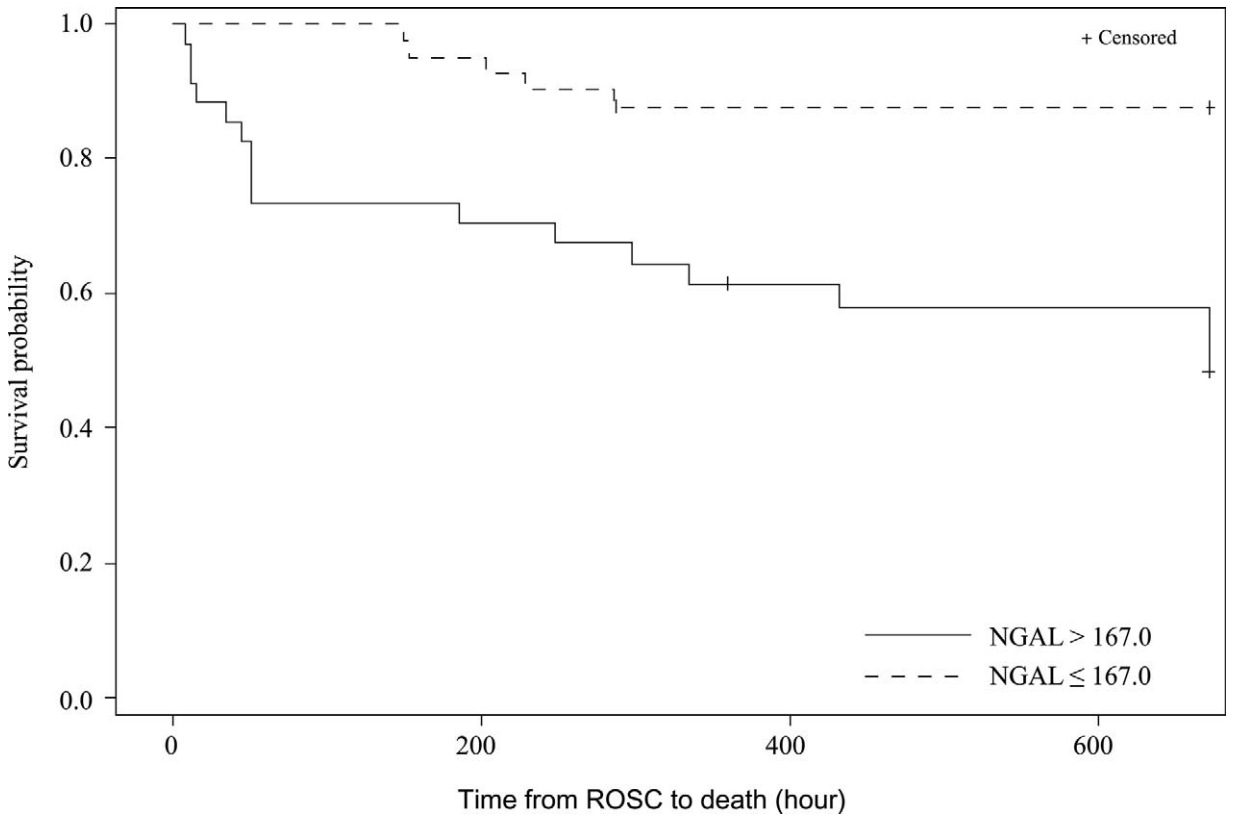

Figure 3. Kaplan–Meier survival curves for 28-day mortality based on the cut-off value of neutrophil gelatinase associated lipocalin (NGAL). ROSC, return of spontaneous circulation.

outcome corresponded to <81.96 ng/ml, and that for 30-day survival to <104.25 ng/ml, when the above mentioned Hitachi conversion formula was applied; these were markedly different from the cut-off values in our study. Plasma NGAL is known to reach its peak level approximately 4 hours after kidney injury.[20] In the study by Park et al, the median sampling time was 142 minutes from ROSC; moreover, the cut-off values in their study were within the reference range of the Hitachi analyzer. We posit that the discrepancy in cut-off values may be explained by NGAL being measured before reaching its peak value in their study. In support of this theory, Elmer et al measured plasma NGAL levels 6 consecutive times within a 72-hour period following ROSC, and calculated AUCs for survival-to-hospital discharge of 0.78 at enrolment and 0.82 at 12 hours after ROSC.[14] However, the study by Elmer et al included both OHCA and IHCA patients, as well as a proportion of subjects not treated with TTM. For this reason, it is not confirmed that the 12-hour NGAL level is the most predictive in OHCA patients treated with TTM; further studies are required to determine the optimal time for serum NGAL measurement that provides the best prediction of outcomes.

In this study, plasma NGAL did not show better predictability compared with traditional prognostic tests; nevertheless, NGAL has several advantages. First, plasma and urinary NGAL can be measured earlier than conventional NSE or S-100β protein to predict the patient's prognosis. Moreover, unlike EEG or SSEP, NGAL is not affected by the medicines used during TTM treatment. These attributes, combined with NGAL testing being straightforward and the results easy to interpret, provide numerous advantages for promoting the wide use of NGAL measurement for predicting prognosis.

There were differences in neurologic outcomes depending on the target temperature among our patients, which is inconsistent with data from a previous study.[21] This discrepancy was presumably caused by the different target temperatures we used depending on the cause of arrest, in accordance with the TTM protocol of our hospital. Patients whose arrests were of cardiac origin, and whose prognosis appeared to be more favorable, were kept below 36°C. Initial rhythm, which is known to be an important prognostic factor, was not associated with prognosis on multivariate analysis. This can be explained by the fact that the time between placing the emergency call and the arrival of the emergency medical personnel on the scene was longer in the shockable rhythm group than in the non-shockable rhythm group (9.3 ± 4.6 vs 7.0 ± 3.1 minutes; $P = .02$). The out-of-hospital CPR time was also longer in the shockable group than in the non-shockable group (17.9 ± 10.9 and 13.9 ± 10.4 minutes, $P = .12$), although the difference was not significant.

This study had several limitations. First, it was conducted at a single center; therefore, the results cannot be generalized more broadly. Second, the plasma NGAL measuring device was changed during the study period, which may have caused differing test results although the conversion formula was used. Third, since the patients' NGAL levels before cardiac arrest are unknown, it is possible that plasma NGAL elevation may have preceded cardiac arrest in some cases; this may increase the false positive rate when predicting prognosis. For example, a patient included in our study experienced cardiac arrest due to

hyperkalemia and AKI; despite a plasma NGAL level of 410 ng/ml (which was higher than the cut-off value), the patient survived and had good neurologic outcome. Therefore, further studies are required to predict the prognosis of cardiac arrest patients who have conditions that predispose them to elevated plasma NGAL before experiencing cardiac arrests. Fourth, patients with end-stage renal disease (ESRD) were excluded because it is yet undetermined whether plasma NGAL is elevated when kidney ischemia occurs in such patients. Therefore, the results of our study cannot be generalized to ESRD patients.

Fifth, it was also difficult to investigate the potential influence of 2 target temperatures on plasma NGAL level in this study, although recent multicenter clinical trials with large sample size have shown that TTM at 33°C or 36°C does not significantly affect NSE or S-100β protein levels.[22,23] Finally, a number of patients who might be considered to be unrecoverable in spite of the delivery of intense care, such as mechanical ventilator care, percutaneous cardiopulmonary support, and high dose vasopressor infusion had withdrawal of life-sustaining therapy and this could inherently affect the outcome measure.

5. Conclusions

Plasma NGAL is valuable for predicting the neurologic outcome and 28-day mortality of patients with OHCA at an early stage after ROSC. Moreover, NGAL can be measured earlier and more easily compared with traditional prognostic tests, and its predictive power is not inferior to that of other indicators except for EEG. If the optimal timing for NGAL measurement is determined via additional studies, we predict that NGAL can be widely used as a prognostic test for OHCA patients who undergo TTM therapy.

Author contributions

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Methodology: Ji Hwan Lee, Yoo Seok Park.
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Writing – original draft: Ji Hwan Lee.
Writing – review & editing: Yoo Seok Park.
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