

# Dynamic Changes of Plasma Neutrophil Gelatinase-Associated Lipocalin Predicted Mortality in Critically Ill Patients with Systemic Inflammatory Response Syndrome

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## Abstract

**Background and Aims:** About 50% of patients admitted to the Intensive Care Unit have systemic inflammatory response syndrome (SIRS), and about 10%–20% of them died. Early risk stratification is important to reduce mortality. Plasma neutrophil gelatinase-associated lipocalin (NGAL) is increased by inflammation and infection. Its ability to predict mortality in SIRS patients is of interest. We evaluated the ability of serial measurement of NGAL for the prediction of mortality in critically ill patients with SIRS. **Materials and Methods:** This is a secondary analysis of a single-center, prospective, observational study. Patients who fulfill the SIRS criteria were recruited in the study. Delta NGAL at 24 and 48 h ( $\Delta$ NGAL-24 and  $\Delta$ NGAL-48) was defined as 24 and 48 h NGAL minus day 1 NGAL; NGAL clearance (NGALc) was defined as percentage of  $\Delta$ NGAL over day 1 NGAL. The primary outcome of the study is in-hospital mortality. **Results:** A total of 151 patients were analyzed, of which 53 (35%) died. Nonsurvivors were older (51 vs. 45,  $P = 0.03$ ) and had higher Sequential Organ Failure Assessment ( $9 \pm 7$  vs.  $7 \pm 4$ ,  $P = 0.02$ ) and Simplified Acute Physiology Score II ( $47 \pm 15$  vs.  $40 \pm 15$ ,  $P = 0.01$ ) scores as compared to survivors. NGAL concentrations over 3 days were higher in nonsurvivors compared to survivors (repeated measures analysis of variance,  $P = 0.02$ ). Day 1 NGAL,  $\Delta$ NGAL-24, and NGALc-24 were not independently predictive of mortality. However, day 3 NGAL,  $\Delta$ NGAL-48, and NGALc-48 were predictive after adjusted for age and severity of illness (odds ratio 9.1 [1.97–41.7]). **Conclusions:** NGAL dynamics over 48 h independently predicted mortality in critically ill patients with SIRS. This could assist clinicians in risk stratification of this group of high-risk patients.

**Key words:** Mortality, neutrophil gelatinase-associated lipocalin, sepsis, systemic inflammatory response syndrome

## INTRODUCTION

About 50% of patients admitted to the Intensive Care Unit (ICU) have systemic inflammatory response syndrome (SIRS).<sup>[1,2]</sup> Of these, 30% have or eventually develop sepsis.<sup>[1,3]</sup> Mortality rates in critically ill patients with SIRS are high, ranging from 10% to 20%. Early risk stratification is important to reduce mortality. This will assist clinicians in reevaluation and intensification of therapy, which could prevent progression of organ failure and the associated increased in mortality.

Neutrophil gelatinase-associated lipocalin (NGAL) is a small molecule of 25 kDa, which is covalently bound to gelatinase from neutrophils and expressed at low concentrations in several human tissues, including kidneys, lungs, stomach, and colon. NGAL binds to iron through its siderophores; it can deplete bacterial iron and plays an important role in immunity to bacterial infection. It also has a role in kidney development and

may promote cellular repair.<sup>[4-7]</sup> NGAL expression is markedly induced by inflammation, such as in acute bacterial infections, severe sepsis and septic shock, asthma or chronic obstructive airway disease, or emphysematous lung.<sup>[6,8,9]</sup>

Plasma NGAL utility in prediction of mortality has been investigated in several studies.<sup>[10-14]</sup> NGAL was not predictive of mortality in three studies.<sup>[10,11,14]</sup> However, in another two studies, NGAL was fairly predictive.<sup>[12,13]</sup> We showed that NGAL was not independently predictive of mortality in our previous study.<sup>[15]</sup> The limitation of that study was that we

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**How to cite this article:** Ralib AM, Nanyan S, Mat Nor MB. Dynamic changes of plasma neutrophil gelatinase-associated lipocalin predicted mortality in critically ill patients with systemic inflammatory response syndrome. *Indian J Crit Care Med* 2017;21:23-9.

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10.4103/0972-5229.198322

only analyzed on admission plasma NGAL concentration. Of interest is how the dynamic of NGAL changes as a tool of mortality prediction as has been shown previously that single measurements of biomarkers were not predictive; however, their dynamic concentrations were predictive.<sup>[16-18]</sup> A further analysis looking at the dynamic of NGAL over several days for prediction of mortality may be of interest.

## MATERIALS AND METHODS

This was a secondary analysis of a single-center, prospective, observational study of Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia. The study was an extension of the BOSS-ICU study,<sup>[18]</sup> registered under the National Medical Research Register (NMR-11-1102-9248). The study was approved by the Medical Research and Ethics Committee. Only patients with available NGAL data measured serially for the first 3 days were included in this analysis. Detail of the NGAL analysis measured on ICU admission has been published elsewhere.<sup>[15]</sup> All consented patients aged above 18 years with established SIRS based on the criteria defined by the American College of Chest Physician/Society of Critical Care Medicine (ACCP/SCCM) were recruited in the study.<sup>[19]</sup> SIRS is defined by the presence of at least two of the following four indicators: (1) A body temperature above 38.0°C or below 36.0°C; (2) a heart rate above 90 beats/min; (3) a respiratory rate above 20 breaths/min; (4) a white blood cell count higher than 12,000 or lower than 4000 cells/ $\mu$ l or more than 10% immature (band) form.<sup>[19]</sup> Consent from legally accepted representative was taken as the patients were mostly unconscious or undergoing resuscitation. Patients with age <18 years, no written consent, or who had received antibiotics for more than 24 h before screening were excluded from the study.

Blood samples were collected within 24 h of ICU admission and daily for 3 consecutive days. The samples were centrifuged at 3600 rpm for 15 min and the plasma were stored at -80°C. Plasma NGAL was analyzed using the Triage® NGAL Test (Biosite, San Diego, USA).<sup>[20]</sup> Plasma electrolytes were analyzed using the Olympus AU2700™ chemistry-immunoanalyzer (Olympus, Philadelphia, USA). NGAL kinetics is expressed as delta NGAL ( $\Delta$ NGAL).  $\Delta$ NGAL at 24 and 48 h ( $\Delta$ NGAL-24 and  $\Delta$ NGAL-48) was defined as 24 and 48 h NGAL minus day 1 NGAL. NGAL clearance (NGALc) at 24 and 48 h (NGALc-24 and NGALc-48) was defined as the percentage of  $\Delta$ NGAL-24 and  $\Delta$ NGAL-48 to day 1 NGAL. The primary outcome of the study is in-hospital mortality.

### Statistical analysis

Statistical analysis was performed using PASW® version 18.0 (IBM, Somers, New York, USA), and PRISM 5.0® (Graph Pad, La Jolla, California, USA). Results are presented as mean  $\pm$  standard deviation for normally distributed variables or median (interquartile range) for nonnormally distributed variables. Comparison of variables between the two groups

was analyzed using independent *t*-test for normally distributed variables or Mann–Whitney test for nonnormally distributed variables. Differences between three groups were analyzed using one-way analysis of variance, with *post hoc* least significant difference analysis. Categorical variables were compared with Chi-square test. The diagnostic and predictive performance of NGAL were assessed by area under the curve (AUC) of receiver operating characteristic (ROC) curve of the sensitivity versus 1-specificity.<sup>[21]</sup> The optimal cutoff point was defined as the measured quantity, which maximized sensitivity and specificity.<sup>[22]</sup> The differences of the AUC were analyzed using DeLong method.<sup>[23]</sup> Survival analysis was performed using Kaplan–Meier and Cox regression survival analyses for calculation of hazard ratios (HRs). All AUC, HR, and integrated discrimination improvement were presented with 95% confidence intervals.

## RESULTS

A total of 151 patients were included in the study. Of these, 53 (35.1%) died in the hospital. Mortality increases with increasing number of SIRS criteria (Chi-square test, *P* = 0.05; Table 1). Comparing between each stage, the differences in mortality were significant only between 2 and 4 SIRS criteria (*P* = 0.04). Table 2 compares the baseline demographic, clinical characteristics, and outcome between patients' survivors and nonsurvivors. Nonsurvivors were older and had higher Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II (SAPS II) scores as compared to survivors.

### Temporal profile of neutrophil gelatinase-associated lipocalin for 3 days

The temporal profile of NGAL between survivors and nonsurvivors is shown in Figure 1. NGAL concentrations were consistently higher in nonsurvivors compared to survivors from day 1 to day 3 (Mann–Whitney test, *P* < 0.04).  $\Delta$ NGAL and NGALc at 48 h ( $\Delta$ NGAL-48 and NGALc-48) were higher in nonsurvivors compared to survivors. In contrast, there were no differences in NGAL kinetics at 24 h [Table 3].

### Prediction of mortality

The AUC of the ROC curve for prediction of mortality is shown in Figure 2 and Table 4. Day 1–3 NGAL were moderately predictive of mortality with AUC of >0.60.

**Table 1: Mortality with number of systemic inflammatory response syndrome criteria**

Number of SIRS criteria	Number of patients	Death, n (%)	<i>P</i>
2	89	25 (28.1)	0.05
3	50	21 (42.0)	
4	12	7 (58.3)	

Data compared using Chi-square test for trends. The differences in mortality between 2 and 3 SIRS criteria was *P*=0.09, between 2 and 4 SIRS criteria was *P*=0.04, and between 3 and 4 SIRS criteria was *P*=0.31. SIRS: Systemic inflammatory response syndrome

NGAL kinetics at 48 h ( $\Delta$ NGAL-48 and NGALc-48) but not 24 h was predictive of mortality. The differences of the AUC between static and dynamic NGAL are presented in Table 5. Of these, the differences between day 1 and day 3 NGAL were significant ( $-0.05$  [ $-0.1$ – $-0.001$ ],  $P = 0.04$ ). For dynamic NGAL, the differences were significant for NGAL kinetics at

24 versus 48 h, with  $P = 0.03$  for both. When comparing static versus dynamic NGAL, differences were only shown for day 3 NGAL versus  $\Delta$ NGAL-24 ( $P = 0.04$ ).

### Multivariate logistic regression analysis for prediction of mortality

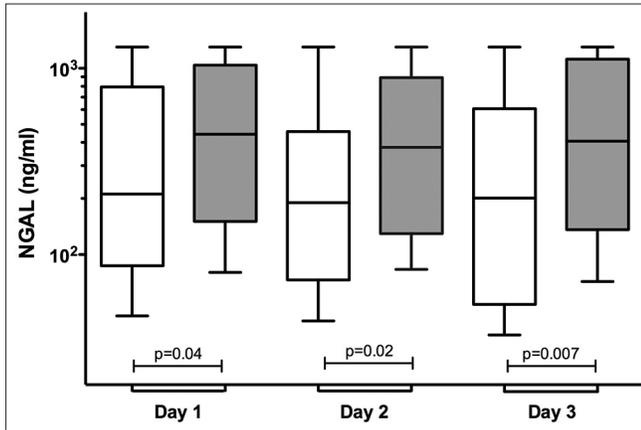
The utility of NGAL and its kinetics for prediction of mortality were further evaluated after adjusting for other covariates. After adjusting for age, presence of acute kidney injury (AKI), and severity of illness (SAPS II), only day 3 NGAL,  $\Delta$ NGAL-48, and NGALc-48 were independently predictive of mortality [Table 6].

### Survival analysis

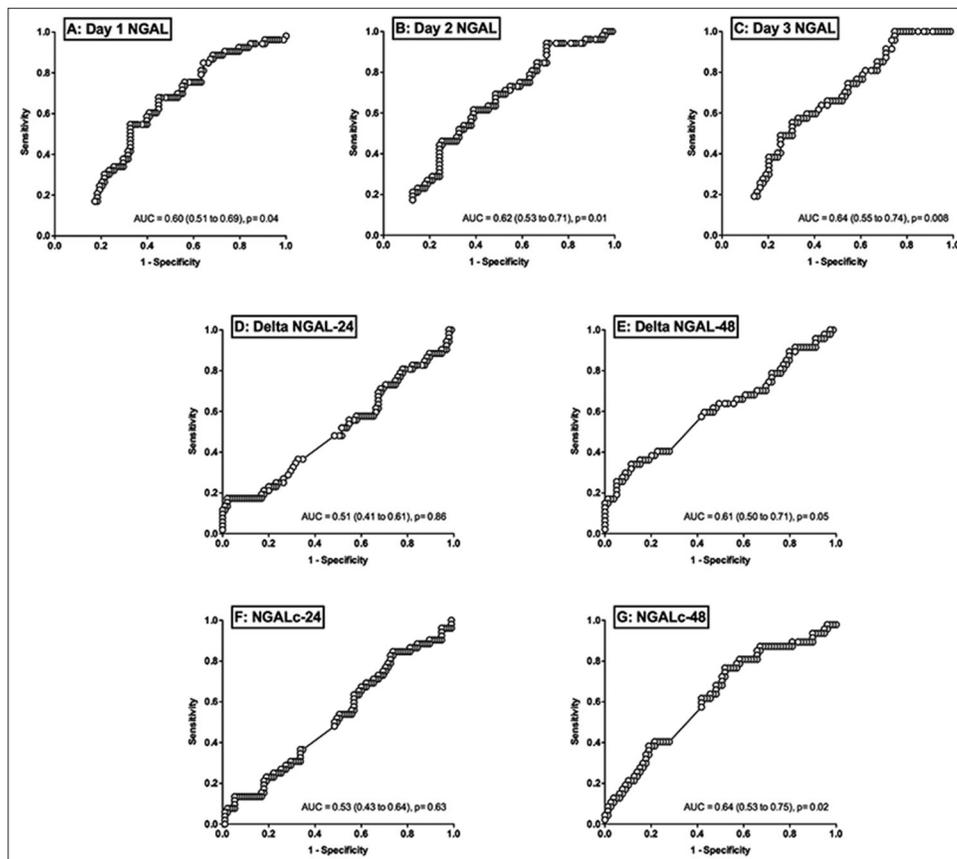
Survival analysis of NGALc-48 at a cutoff point of  $-24\%$  was analyzed [Figure 3]. There was lower survival in patients with NGALc at 48 h of more than  $-24\%$  compared to those with lower cutoff point (log Mantel-Cox,  $P = 0.03$ ). After adjusted for age and severity of illness, patients with NGALc-48 more than  $-24\%$  were twice more likely to die at 30 days compared to those less than the cutoff point (Cox regression analysis, odds ratio 2.10 [1.05–4.18],  $P = 0.03$ ).

### DISCUSSION

In this prospective study, we showed that day 3 NGAL and NGAL kinetics at 48 h were independently predictive of



**Figure 1:** Temporal profiles of plasma neutrophil gelatinase-associated lipocalin concentration between survivors and nonsurvivors within the first 3 days of Intensive Care Unit admission. Mann-Whitney test,  $P = 0.04$  (day 1),  $P = 0.02$  (day 2), and  $P = 0.007$  (day 3). Repeated Measures analysis of variance showed the difference between subjects,  $P < 0.0001$ , and within subjects,  $P = 0.28$ .



**Figure 2:** The area under the curve of the sensitivity over 1-specificity curve for static and dynamic neutrophil gelatinase-associated lipocalin concentration.

**Table 2: Demographics and clinical characteristics between survivors and nonsurvivors**

Variables	All patients (n=151)	Survivors (n=98)	Nonsurvivors (n=53)	P
Age (years)	47±17	45±17	51±16	0.03
Gender (male)	98 (64.9)	65 (66.3)	33 (62.3)	0.83
Weight (kg)	67±13	67±11	66±15	0.75
Height (cm)	161±8	162±9	161±7	0.43
Baseline SAPS II	43±15	40±15	47±15	0.01
Baseline SOFA score	8.0±4.0	7.4±4.0	9.1±3.8	0.02
Category				
Noninfectious SIRS	64 (42.4)	43 (43.9)	21 (39.6)	0.61
Sepsis	87 (57.6)	55 (56.1)	32 (60.4)	
Category				
Medical	90 (59.6)	55 (56.1)	35 (66.0)	0.24
Surgical	61 (40.4)	43 (43.9)	18 (34.0)	
Primary admission diagnoses				
Cardiovascular	4 (2.7)	3 (3.0)	1 (1.9)	0.65
Endocrine/metabolic	4 (2.6)	3 (3.1)	1 (1.9)	
Gastrointestinal/ hepatobiliary/pancreas	17 (11.3)	12 (12.2)	5 (9.4)	
Infective	26 (17.2)	17 (17.3)	9 (17.0)	
Renal	4 (2.6)	2 (2.0)	2 (3.8)	
Neurological	18 (11.9)	7 (7.1)	11 (20.8)	
Respiratory	48 (31.8)	33 (33.7)	15 (28.3)	
Trauma	25 (16.6)	18 (18.4)	7 (13.2)	
Connective tissue/ autoimmune	2 (1.3)	1 (1.0)	1 (1.9)	
Other	3 (2.0)	2 (2.0)	1 (1.9)	
Comorbidity				
Diabetes mellitus	40 (26.5)	24 (24.5)	16 (30.2)	0.45
Hypertension	47 (31.1)	31 (31.6)	16 (30.2)	0.86
Chronic kidney disease	5 (4.8)	4 (6.3)	1 (2.4)	0.35
Chronic lung disease	20 (13.2)	13 (13.3)	7 (13.2)	0.99
Chronic cardiovascular disease	3 (2.0)	1 (1.0)	2 (3.8)	0.25
Immunosuppression	2 (1.3)	0 (0)	2 (3.8)	0.05
Others	11 (7.3)	4 (4.1)	7 (13.2)	0.04
Dialysis	30 (19.9)	17 (17.3)	13 (24.5)	0.29

Data expressed as mean±SD, n (%), or median (lower quartile-upper quartile. Other comorbidities are other disabling conditions which may include hypothyroidism, hyperthyroidism, joint diseases, mental health, etc., ). SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome

**Table 3: Neutrophil gelatinase-associated lipocalin concentrations and Δ neutrophil gelatinase associated lipocalin between survivors and nonsurvivors**

	Survivors (n=98)	Nonsurvivors (n=53)	P
Day 1 NGAL (ng/ml)	212 (87-795)	443 (150-1040)	0.04
Day 2 NGAL (ng/ml)	190 (73-458)	377 (130-891)	0.02
Day 3 NGAL (ng/ml)	201 (54-607)	406 (136-1120)	0.007
ΔNGAL-24 (ng/ml)	-63±197	-50±268	0.75
ΔNGAL-48 (ng/ml)	-76±174	16±232	0.01
NGALc-24 (%)	-4.1±5.2	5.2±63	0.32
NGALc-48 (%)	-9.6±51	26±109	0.01

Data expressed as mean±SD, or median (lower quartile-upper quartile). NGAL: Neutrophil gelatinase-associated lipocalin; NGALc: Neutrophil gelatinase-associated lipocalin clearance; SD: Standard deviation

mortality in critically ill patients with SIRS. In contrast, plasma NGAL measured on ICU admission was not independently predictive of mortality. Patients with NGALc at 48 h at a cutoff point of -24% were twice more likely to die compared to those at a lower cutoff point.

SIRS is due to widespread inflammation secondary to infectious or noninfectious cause. It is common in intensive care settings, occurring in more than 50% of patients admitted to the ICU,<sup>[1]</sup> higher in surgical ICU.<sup>[2]</sup> About one-third of SIRS patients have or eventually develop sepsis, and about 10%-20% died.<sup>[1,3]</sup> In our study, mortality was higher occurring in about 30% of our patients with SIRS. Mortality rate increases as the number of SIRS criteria increases.<sup>[24]</sup> Similarly, we showed that mortality occurred in 58% of patients with 4 SIRS criteria compared to 42%

**Table 4: Area under receiver operating characteristics curve for prediction of mortality**

	AUC (95% CI)	Optimal cut-off point	Sensitivity	Specificity	PPV	NPV
Day 1 NGAL	0.60 (0.51-0.69)	222	68 (55-81)	55 (45-65)	45 (34-56)	76 (66-86)
Day 2 NGAL	0.62 (0.53-0.71)	278	62 (48-75)	61 (51-71)	46 (35-58)	74 (65-84)
Day 3 NGAL	0.64 (0.55-0.74)	319	57 (43-72)	67 (57-77)	51 (37-64)	73 (62-83)
ΔNGAL-24	0.51 (0.41-0.61)	-14	50 (36-64)	52 (42-63)	37 (25-49)	65 (54-77)
ΔNGAL-48	0.61 (0.50-0.71)	-6	49 (33-64)	74 (63-84)	51 (35-67)	71 (61-82)
NGALc-24	0.53 (0.43-0.64)	-12	59 (44-73)	50 (39-61)	40 (28-51)	68 (57-80)
NGALc-48	0.64 (0.53-0.75)	-24	72 (58-86)	54 (42-65)	47 (34-59)	77 (65-89)

Data presented with 95% CI. AUC: Area under curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; NGAL: Neutrophil gelatinase-associated lipocalin; NGALc: Neutrophil gelatinase-associated lipocalin clearance

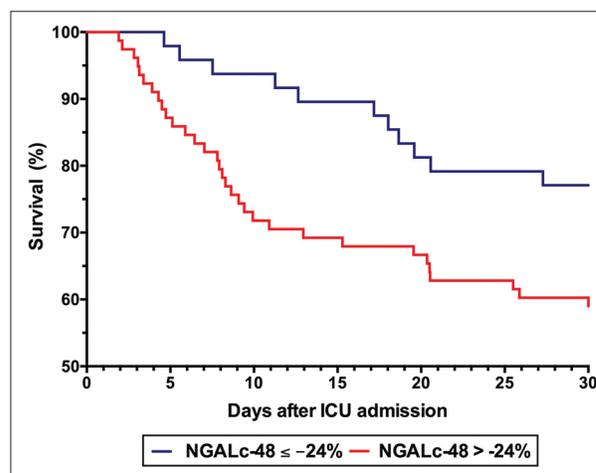
**Table 5: The differences in the area under curve between static and kinetic of neutrophil gelatinase-associated lipocalin**

Comparison of AUC between		Differences in AUC	P
<b>Static NGAL</b>			
Day 1 NGAL	Day 2 NGAL	-0.02 (-0.06-0.03)	0.46
	Day 3 NGAL	-0.05 (-0.1--0.001)	0.04
Day 2 NGAL	Day 3 NGAL	-0.04 (-0.09-0.01)	0.15
<b>Dynamic NGAL</b>			
ΔNGAL-24	ΔNGAL-48	0.12 (0.01-0.23)	0.03
	NGALc-24	0.02 (-0.02-0.05)	0.44
NGALc-24	NGALc-48	0.12 (0.01-0.23)	0.03
ΔNGAL-48	NGALc-48	0.02 (-0.02-0.07)	0.48
<b>Static versus dynamic NGAL</b>			
Day 1 NGAL	ΔNGAL-24	-0.09 (-0.24-0.06)	0.24
	ΔNGAL-48	0.02 (-0.14-0.18)	0.80
	NGALc-24	-0.08 (-0.23-0.08)	0.33
	NGALc-48	0.04 (-0.12-0.2)	0.61
Day 2 NGAL	ΔNGAL-24	-0.11 (-0.24-0.014)	0.08
	ΔNGAL-48	-0.003 (-0.15-0.14)	0.97
	NGALc-24	-0.10 (-0.22-0.03)	0.12
	NGALc-48	0.016 (-0.13-0.16)	0.82
Day 3 NGAL	ΔNGAL-24	-0.15 (-0.3--0.008)	0.04
	ΔNGAL-48	-0.03 (-0.16--0.10)	0.63
	NGALc-24	-0.14 (-0.28-0.005)	0.06
	NGALc-48	-0.01 (-0.13-0.1)	0.82

Comparison of AUC was analyzed using DeLong method. NGAL: Neutrophil gelatinase-associated lipocalin; NGALc: Neutrophil gelatinase-associated lipocalin clearance; AUC: Area under curve

in those with 3 SIRS criteria and 28% with 2 SIRS criteria. The differences in mortality were significant between 2 and 4 SIRS criteria ( $P=0.04$ ). Hence, early risk stratification in SIRS patients is important to reduce mortality. This could alert an intensivist for reevaluation or intensification of therapy, for example, early dialysis, modification of antimicrobial therapy, or the need for additional diagnosis measures, which could prevent progression of organ failure and the associated increased in mortality.<sup>[18]</sup>

Biomarkers could assist in risk stratification of critically ill patients. Plasma NGAL is a small molecule of 25 kDa. It has



**Figure 3:** Survival analysis of neutrophil gelatinase-associated lipocalin clearance at 48 at a cutoff point of  $-24\%$ . Patients with neutrophil gelatinase-associated lipocalin clearance at 48 h of more than  $-24\%$  were more likely to die within 30 days compared to those with lower cutoff point (log Mantel-Cox,  $P = 0.03$ ).

been investigated as a biomarker of sepsis<sup>[13]</sup> and AKI and prediction of mortality.<sup>[14,15,17]</sup> Most studies investigated the value of single time point measurement of biomarker. This may be of limited value due to variability of biomarker secretion at different phases of critical illness and unknown time lapsed between insult and ICU admission.<sup>[18]</sup> We showed that plasma NGAL measured on ICU admission was not predictive of mortality after adjusting for age, presence of AKI, and severity of illness. In contrast, plasma NGAL measured after 48 h was independently predictive with an odds ratio of 2.58 (1.26–5.29). AKI was included as covariates as it correlates with an increase in NGAL concentration.<sup>[14]</sup>

We showed that day 3 NGAL and NGAL kinetics at 48 h were moderately predictive of mortality with AUC of  $>0.60$ . The AUC is a measure of discrimination that is how well a given test (e.g., a new biomarker) separates those with and without disease as determined by the gold standard.<sup>[25]</sup> It ranges from 0.5 (no discrimination) to 1 (perfect discrimination).<sup>[25,26]</sup> Clinical validity is assumed at an AUC of more than 0.70. Hence, AUC of day 3 NGAL and NGAL kinetics at 48 h of 0.64 is not assumed to be predictive of mortality. In addition,

**Table 6: Multivariate analysis for prediction of mortality**

Variables	OR (95% CI)	P
Age	0.97 (0.93-1.02)	0.29
SAPS II (without renal score)	1.09 (1.00-1.18)	0.06
Acute kidney injury	3.60 (0.63-20.6)	0.15
Day 1 NGAL	1.59 (0.70-3.64)	0.27
Day 2 NGAL	2.14 (0.86-5.35)	0.10
Day 3 NGAL	3.64 (1.41-9.37)	0.007
$\Delta$ NGAL-24	1.70 (0.54-5.34)	0.37
$\Delta$ NGAL-48	12.0 (1.97-73.4)	0.007
NGALc-24	2.15 (0.57-8.16)	0.26
NGALc-48	5.34 (1.11-25.6)	0.04

All NGAL values are log-transformed. Data expressed as OR with 95% CI. Acute kidney injury defined by creatinine >50% of first admission creatinine or urine output of <0.5 ml/kg/h for 6 h. NGAL data were entered separately. NGAL: Neutrophil gelatinase-associated lipocalin; NGALc: Neutrophil gelatinase-associated lipocalin clearance; OR: Odds ratio; CI: Confidence interval; SAPS: Simplified Acute Physiological Score

differences between the AUC of static versus dynamic NGAL was only significant between day 3 and  $\Delta$ NGAL-24. However, the main limitation of the AUC is that its calculation is based on rank, merely considering the comparative rank between those with and without the disease. It does not take into account the extent of change of the biomarker or its distribution. Any change of rank in those at low distribution will have the same impact in those at high distribution.<sup>[25]</sup>

The additional value of a new biomarker to an available clinical diagnostic or predictor assessment (the reference model) may be better assessed by the multivariate logistic regression analysis. NGAL kinetics has an added value in reference to the SAPS II for prediction of mortality. This is shown in the multivariate logistic regression analysis which showed that NGAL kinetics at 48 h predicted mortality even after adjusted for SAPS II. We did not include both SOFA and SAPS II as both contain almost similar parameters and are strongly correlated ( $r = 0.718$ ,  $P < 0.0001$ ).

Serial measurement of biomarker allows assessment of dynamic changes. Dynamic changes of biomarker had been shown to better predict outcome such as mortality compared to a single time point collection. The added value of calculating the dynamic changes of biomarker is that it integrates change over time, which captures function of both severity and duration of injury. Dynamic changes of creatinine, procalcitonin, and urinary cystatin C had been shown to be predictive of outcome.<sup>[16-18]</sup> The extent of changes in NGAL may be influenced by its baseline concentration as has been shown previously that NGAL was higher in patients with sepsis compared to SIRS.<sup>[13,15]</sup> To adjust for this, we calculated the relative changes of NGAL in relation to day 1 plasma NGAL. We showed that both the actual and relative dynamic changes of NGAL after 48 h were independently predictive of mortality.

The cutoff point of NGALc or its dynamic changes is of interest as this could assist clinicians in identifying at-risk patient. We

showed that patients with 48 h NGALc of more than -24% were twice more likely to die compared to those with clearance of less than the cutoff point. From this, we suggest that NGAL could be measured on admission and repeated 48 h later to assist in identifying at-risk patients who may benefit from reevaluation and intensification of therapy.

### Study limitations

The study has several limitations. First, it was conducted at a single center with a small sample size. Second, the strict inclusion criteria of patients with SIRS in this study limit generalizability of the finding to other patient groups in the ICU. Finally, NGAL was measured within 24 h of ICU admission. Measurement within 2–4 h may capture earlier changes that occur with the kidney cellular injury. However, a study had shown that there was no difference in NGAL performance when measured earlier at the emergency department or later in the ICU.<sup>[14]</sup>

### CONCLUSIONS

NGAL kinetics and its dynamics over 48 h were independently predicted mortality in critically ill patients with SIRS. Patients with NGALc at 48 h at a cutoff point of more than -24% were twice more likely to die compared to those at a lower cutoff point. This could assist clinicians in risk stratification of this group of high-risk patients.

### Acknowledgments

We would like to thank Siti Nabilah Zainuddin, Hismayanti Ghazali, Diana Hafiza Ghazali, and Nurhafizah Zairudin for their assistance in data collection for the study. Abstract of this presentation has been presented at the Malaysian Society of Anaesthesiologists Annual Scientific Congress 2016 and has been awarded with the MSA Award 2016.

### Financial support and sponsorship

This study was funded by the Ministry of Higher Education Fundamental Research Grant Scheme (FRGS/1/2015/SKK02/UIAM/02/3).

### Conflicts of interest

There are no conflicts of interest.

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