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The validity of urinary neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker of acute kidney injury in pediatric patients with sepsis

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Abstract

***Background*: Septic patients with acute kidney injury (AKI) are associated with increased morbidity and mortality compared to septic patients without AKI. These usually occur within 24 hours of admission into ICU. The measurement of serum creatinine is usually used to diagnose AKI. However, the concentrations do not change until a decline in kidney function has reached 50% or less within a few days. Many studies have shown urinary neutrophil gelatinase-associated lipocalin (NGAL) as a predictor of AKI with different cut-off points.**

***Objective*: This study aimed to determine the cut-off point of urinary NGAL in predicting the occurrence of AKI in pediatric septic patients within 48 to 72 hours after being admitted into ICU.**

***Methods*: This was an observational analytic study with prospective longitudinal design, carried out on patients who met the inclusion and exclusion criteria at the resuscitation room in the Emergency Room (ER) at Dr. Soetomo Hospital Surabaya. The urine was taken at the 0th, 6th, 12th, and 24th hours for urinary NGAL examination. Every procedure taken on each patient was recorded and followed until the third day to determine factors correlated with AKI.**

***Result*: Of the total 41 pediatric septic patients, 30 met the inclusion and exclusion criteria and about 56.7% had AKI. The urinary NGAL at 0th hour had significant value. A cut-off point of 1242 ng/ml was a better determinant of the incidence of AKI with a sensitivity of 76.5%, specificity of 61.5%, area under the curve (AUC) of 0.715, and relative risk of 2.2. Furthermore, the urinary NGAL at 0th hour was able to differentiate each level of AKI. Yet, the urine values of NGAL at 6th, 12th, and 24th hours were invalid as predictor of AKI.**

***Conclusion*: Urinary NGAL at 0th hour is a valid predictor of occurrence of AKI grades 1, 2, and 3 in pediatric septic patients 48-72 hours after being admitted into the hospital.**

Key words: Pediatric patient with sepsis, acute kidney injury, urinary NGAL.

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Introduction

Sepsis is a syndrome of dysregulated response to infection in the body. Sometimes, it leads to death from most diseases worldwide. (1) It causes acute kidney injury (AKI) associated with increased morbidity and mortality compared to non-septic AKI in adults, and this usually occurs within 24 hours of admission into the intensive care unit. (2-4) In the modern clinical practice, AKI is usually diagnosed by measuring the serum creatinine. However, the concentration of serum creatinine might not change until the kidney function decreases by 50% within few days. (5) Therefore, it needs a biomarker with the ability of detecting it

early. Hence, the most studied and promising biomarker in pediatric acute kidney disorders is neutrophil gelatinase-associated lipocalin (NGAL).

Several studies related to AKI conducted on several species such as rats and humans have consistently shown NGAL to be one of the most common biomarkers found in the kidney immediately after ischemic or nephrotoxic events. (6,7) NGAL is also widely produced in the regeneration and recovery of renal tubular cells. (8) It binds iron to aid toxic iron-chelating process, that is an important mechanism in the protection of kidney tubules from worsening injuries. Thus, NGAL can be used as a biomarker in predicting acute renal impairment and its poor outcome regardless of serum creatinine levels. (9)

In the past decade, the focus on the role of NGAL has shifted from just an undifferentiated systemic inflammation marker to a real marker for early detection of AKI. This is due to some research showing NGAL as one of the genes most rapidly regulated after acute ischemic kidney injury in animals. Some studies have also verified the induction of NGAL protein in the kidneys after ischemic and nephrotoxic kidney injury, with its urine concentration increasing several folds within a few hours after injury. (8) In addition, NGAL is useful as an early marker of AKI when kidney damage has not been known yet and it is able to diagnose AKI ≤48 hours before a clinical diagnosis of acute kidney injury is made based on consensus definition. (10)

Studies in critically ill patients have consistently shown an association between plasma or urine levels and the severity of AKI. (11-13) Urinary NGAL is not detected before ischemia but it starts to show in urine 2-3 hours after the condition occurs. The time of occurrence, intensity, and duration of NGAL urine expression is related to the incidence of ischemia. The maximum NGAL level in AKI is about 1000 times in urine and 300 times in blood. (8,14) In animal trials, its urine levels during AKI are more accurate than serum creatinine. Therefore, it is concluded that the majority of urinary NGAL is produced from ischemic kidneys. (15)

Moreover, another study evaluating the use of NGAL as a predictor of AKI evolution was performed in children undergoing cardiac surgery. The urinary NGAL increased almost 100 times, and serum NGAL 20 times up to 48 hours before the AKI was detected by creatinine. (16) It assists children undergoing cardiopulmonary bypass, as its measurements in the urine and blood are beneficial in identifying early patients at risk of AKI. Yet, some studies showed a delay of 1-3 days in the diagnosis of AKI when serum creatinine was used as a gold standard marker. (16-18) Research in pediatric septic patients showed that the value of urinary NGAL was not affected by sepsis and that serum NGAL did not distinguish patients with or without AKI. (19) Furthermore, studies conducted on critically ill patients showed that urinary NGAL had the capacity of predicting the occurrence of AKI better than serum NGAL. (20)

Therefore, this study aimed to determine the cut-off point of urinary NGAL in predicting the occurrence of AKI in pediatric septic patients within 48 to 72 hours of being admitted into ICU.

Material and method

Study design and setting

The approval of this research was granted by the Institutional Ethics Committee (Dr. Soetomo General Hospital Surabaya, Indonesia). Besides, every pediatric patient admitted to the resuscitation room from October to December 2019, were evaluated. This resuscitation room was only for blue coded patients based on Canadian triage criteria. Also, 41 pediatric patients were enrolled in this prospective observational study with their consents fully obtained through a written informed consent.

Selection criteria for participants

The following criteria were set for the participants enrolled into the study: pediatric patients aged over 3 months - 18 years, with suspected diagnosis of sepsis. While septic shock was assessed according to the Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score criteria by Consensus on Sepsis Management in Pediatrics. The method of total sampling selection of all pediatric patients treated in the rescucitaton room was used to select the participants. Each patient's guardian was given information for consent and obtained enrolled as a subject upon agreeing. The exclusion criteria included: 1) patients with pre-existing kidney disease, 2) patients with pre-existing heart disease, 3) patients with malignancy, intoxication history, infection, 4) diagnosed sepsis at a previous hospital, 5) PELOD-2 score <7.

Exposure and outcome

The patients received a standard protocol for pediatric sepsis management after being admitted to the resuscitation room. Furthermore, the baseline clinical conditions such as arterial blood pressure, heart rate, respiratory rate, temperature, capillary refill time, Glasgow coma scale, and pulse were all recorded for processing. The amount of fluid input and output for 72 hours, inotropic drugs, vasopres-

sors, and ventilator used were also recorded. The laboratory examinations conducted consisted: complete blood count, liver function test (serum glutamic oxaloacetic transaminase [SGOT]/serum glutamic pyruvic transaminase [SGPT]), hemostasis test (prothrombin time [PT]/activated partial thromboplastin time [aPTT]), blood gas analysis (BGA), renal function test (blood urea nitrogen [BUN]/serum creatinine), lactate, procalcitonin, blood culture, and urinary NGAL. However, the NGAL examination was performed at 0th, 6th, 12th, and 24th hours of admission into the emergency room. For routine NGAL examinations, 2 ml of urine specimens were taken from the urine catheter. While extracting the sample, the urine inside the catheter was discarded previously in order to obtain the appropriate sample. However, a "post-resc." statement was usually written whenever the urine fails to come out during examination, it meant post-resuscitation. The examination of urine and plasma samples was performed by enzyme-linked immunosorbent assay (ELISA) (indirect) using the NGAL Elisa Kit. In addition, serum creatinine and BUN in the blood samples were reported at 0th, 24th, 48th, 72th, and 96th hours of arrival. The patients were also evaluated for grades 1, 2, and 3 AKI and without AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Statistical analysis

Statistical analysis was performed using the SPSS software version 25. The continuous variables were expressed as mean±standard deviation (SD) or median (range), and compared using the t-test or Mann-Whitney test. While the categorical variables were expressed as absolute number and proportions (%) and compared using chi-square or Fisher exact test. The cut-off determination used the receiver operator characteristic (ROC) curve and area under the curve (AUC) determined its validity. The sensitivity, specificity, positive, and negative predictive values, as well as the positive and negative likelihood ratios were calculated. Besides, the kappa association and Mc Nemar comparison tests were conducted in this study.

Results

The results showed that of the 41 pediatric patients with sepsis who were treated early in the resuscitation room, 11 patients died in less than 24 hours. Hence, the remaining 30 patients who met the criteria were sampled. Furthermore, the incidence of AKI among these remaining patients was 56.7%. For the groupings, 13 patients were in group I (non-AKI) while the remaining 17 were in group II (AKI grades 1-3). The demographic parameters, early assessment, therapy characteristic, and outcome are all presented in **Table 1**.

Data were presented as mean, median, range, frequency, and percentage. There was no significant statistical difference in the demographic data between the two groups.

Majority of the patients admitted in this study met the criteria of a decrease in creatinine clearance with a significant p value ($p<0.001$) as shown in **Table 2**. Next, there was decreased creatinine clearance criteria in patients who met both criteria. This study further showed that there was normal urine output in some of the patients with kidney failure who were routinely dialyzed.

Based on **Table 3**, the most significant value of urinary NGAL in the comparison between non-AKI and AKI grade 1-3 patients was at the 0th hour. Besides, a comparison chart of the median values between the non-AKI and AKI patients is presented in **Figure 1**. It shows that the median NGAL value between patients with and without AKI was different, although it was not statistically significant. Furthermore, a ROC curve drawn to determine the AUC for NGAL at 0th hour as a predictor for AKI in each grade of AKI to determine the AUC and assessed the significance, as shown in **Table 4** and **Figure 2**. The p values obtained were significant predicting AKI grades 1, 2, and 3 ($p=0.047$); grades 2 and 3 ($p=0.028$); and grade 3 only ($p=0.017$).

In the diagnostic test for the 0th hour, the cut-off point at 2119 and 2603 ng/ml for AKI grade 1, 2, and 3 with 95% CI obtained a sensitivity of 58.8-64.7% and specificity of 61.5%. However, the graph in **Figure 3** shows that the specificity of 61.5% had a sensitivity varied from 52.9 to 82.4%. Therefore, the cut-off point used in this study was the one with the highest sensitivity of 1242 ng/ml.

The results of the diagnostic test in **Table 5** shows a positive predictive value of 72.2%, the negative predictive value of 66.7%, and a relative risk of 2.2. This means that patients with urinary NGAL≥1242 ng/ml had a risk of experiencing AKI grades 1, 2, and 3 by 2.2 times higher than patients with urinary NGAL value <1242 ng/ml. Moreover, urinary NGAL diagnostic test at 0th hour had a cut-off point at 3361 ng/ml for AKI grades 2 and 3 incidence with 95% CI achieved an 80% sensitivity and 72% specificity. Furthermore, a cut-off point of 3834 ng/ml was obtained in predicting the incidence of AKI grade 3 (95% CI, sensitivity of 100% and a specificity of 88.9%).

Discussion

The diagnosis of AKI currently used the gold standard, that was the estimated creatinine clearance and urine output. (21) Estimation of creatinine clearance would only show abnormalities after kidney function drops to 50% or more. (22) Hence, creatinine clearance is less reliable because it is influenced by many factors other than the kidney issue such as age, sex, muscle mass, and examination methods. (23)

The demographic data showed variations in age difference between the non-AKI compared to the AKI group. The median age of patients with AKI was younger compared to those without AKI. This variation was in line with previous studies, in which the incidence of sepsis in pediatric patients was highest in infants, that then decreased by age. (13,19,24,25)

In addition, there are more male patients experiencing sepsis both with and without AKI, and this corresponded to the results of other studies. (25-27) The PELOD-2 scores in both non-AKI and AKI grade 1 to 3 patients had a median of 11 and 12, respectively, with the same range of 7 to 17, that was in line to a global study with an average PELOD-2 score of 11 and range of 2 to 12. (26)

The initial lactate of the AKI group had a higher median compared to the non-AKI group; 2.2 mmol/l and 1.71 mmol/l, respectively. This median was in line with a previous study where patients with severe AKI had a higher lactate value. (26) Abdominal infections were the initial and most common diagnosis of organ with AKI, followed by shock. Shock is as a result of ischemia, which results in decreased perfusion to the tissues. (26)

In terms of therapy, the ventilator was mostly used for pediatric septic patients with AKI. This finding corresponded with other studies in which the percentage of patients using ventilators were higher in the AKI group. (19,26) The use of vasopressors, inotropes, and fluid resuscitation were also given to the pediatric septic patients with AKI. Similar results were obtained by Fitzgerald and colleagues, as well as a research by Di Nardo and colleagues. (19,26)

In addition, the duration of intensive care and total hospital length of stay of the patients with AKI was longer than those without AKI. This was in line with a previous study showing that the length of stay of pediatric septic patients with AKI was longer. (26) Another early study on potential biomarkers of urine fibroblast growth factor-2 and epithelial growth factor in critically ill children with AKI showed that the mortality of pediatric septic patients with AKI was higher than those without AKI. (28) Other previous studies had also shown greater mortality in pediatric septic patients with severe AKI. (26-28)

In this study, the value of urinary NGAL in the AKI group was significant at 0th hour. Therefore, urinary NGAL at 0th hour was able to differentiate each grade of AKI based on KDIGO criteria. This was in line with a study conducted by Zwiers and colleagues in 2015, in which the urinary NGAL examined at 0-6th hour was used to distinguish patients with AKI that occurred within 48 hours from non-AKI. (27) Considering the ROC curve in this study, urinary NGAL at the 0th hour was capable of effectively stratifying AKI in pediatric septic patients.

The urinary NGAL cut-off point from this study was compared with another study of similar cut-off point, although Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria was used for the diagnosis of AKI, as shown in **Table 6**. (29)

The urinary NGAL in septic patients was usually high. (30) Based on the results obtained in another study, the maximum value of urinary NGAL was highest in septic patients' group. (27) However, the urinary NGAL cut-off value in this study was higher compared to other studies. In addition, the urinary NGAL decreased by time, that could be a sign of improvement in the patient's condition. (27) Furthermore, the urinary NGAL at the 0th hour did not show increased mortality by increasing urinary NGAL. It means that a high urinary NGAL value did not have the capacity of predicting mortality for more than 24 hours, hence, examining pediatric septic patients with high urinary NGAL always resulted in poor prognosis.

Study limitations

There were some limitations to this study. The urinary NGAL could not be used as a single parameter to determine the case of AKI due to its high value in pediatric septic patients, but it was not too high in other patients. (27) However, a study by Khasani and colleagues showed that the urinary NGAL value in adult septic patients had the highest variation compared to other patients and other biomarkers. (30) It was also shown in this study that NGAL could be used to indicate the severity of the disease in intensive care patients. (31,32) Such patients tended to have a strong inflammatory response due to injuries in several organs, exposure to repeated invasive procedures, fluid therapy and vasopressor support, blood transfusion, and several other biological modifiers. Network-specific biomarkers were biased by these confounders. (33)

Furthermore, NGAL is a biomarker developed for assessing kidney function, though more expensive than other biomarkers. (20) This is a single-centered research, however, there is need for multi-centered studies to obtain a better accuracy of urinary NGAL as a predictor of AKI.

Conclusion

Conclusively, the urinary NGAL at 0th hour with a cut-off of 1242 ng/ml is a valid predictor of AKI grades 1, 2, and 3 in pediatric septic patients within 48-72 hours based on KDIGO criteria. However, the cut-off point is higher because NGAL is also produced by organs besides the kidney.

Table 1. The demographic parameters, early assessment, therapy, and outcome of the patients

Parameters	Group I (n=13) Non-AKI	Group II (n=17) AKI grades 1-3	p value
Demographic			
- Age (months), median (range)	22 (8-67)	11 (3-86)	0.232*
- 3 months - 1 year old, n (%)	4 (30.8)	10 (58.8)	0.306***
- 1 - 5 years old, n (%)	8 (61.5)	6 (35.3)	
- 5 - 10 years old, n (%)	1 (7.7)	1 (5.9)	
- Male, n (%)	9 (69.2)	12 (70.6)	1.000*
- PELOD-2 score, median (range)	11 (7-17)	12 (7-17)	0.32*
- Early lactate, median (range)	1.71 (0.64-7.14)	2.2 (0.7-7.6)	0.983*
Early assessment			
- Pneumonia, n (%)	4 (30.8)	7 (41.2)	0.708**
- Shock, n (%)	5 (38.5)	11 (64.7)	0.269**
- Meningo/encephalitis, n (%)	7 (53.8)	9 (52.9)	1.000**
- Diarrhea/gastroenteritis, (%)	9 (69.2)	12 (70.6)	1.000**
Therapy characteristics			
- Ventilator, n (%)	11 (84.6)	17 (100)	0.179**
- Fluid resuscitation, n (%)	11 (84.6)	16 (94.1)	0.565**
- Inotropic agents, n (%)	5 (38.5)	8 (47.1)	0.721**
- Diuretic agents, n (%)	0 (0)	2 (11.8)	0.492**
Outcome			
- Ventilator (days), median (range)	4 (0-16)	4 (1-34)	0.445*
- Ventilator free (days), median (range)	6 (0-1275)	5 (0-75)	0.502*
- PICU LOS (days), median (range)	4 (2-16)	6 (1.5-34)	0.487*
- Total LOS (days), median (range)	7 (2-31)	12 (1.5-37)	0.389*
- Mortality, n (%)	4 (30.8)	8 (47.1)	0.465**

Legend: PELOD-2=Pediatric Logistic Organ Dysfunction 2; PICU=pediatric intensive care unit; LOS= length of stay; AKI=acute kidney injury; *Mann-Whitney test; **Fisher-exact test; ***Chi-square test.

Table 2. Comparison of AKI diagnosis based on KDIGO criteria

AKI	n (%)	p value
Met decreased creatinine clearance criteria only	8 (47.1)	<0.001*
Met urine output criteria only	5 (29.4)	
Met both criteria - Decreased creatinine clearance criteria dominating - Urine output criteria dominating - Same score in both criteria	4 (23.5) 2 (11.8) 1 (5.9) 1 (5.9)	

Legend: AKI=acute kidney injury; KDIGO=Kidney Disease: Improving Global Outcomes; *Chi-square test.

Table 3. Comparison of urinary NGAL median value and AKI

NGAL (hour)	Non-AKI (n=13)	AKI grades 1-3 (n=17)	p value
0th	1024 (77.9-3830)	2785 (326.4-4194)	0.047
6th	402.2 (52-4948)	2600 (205-4332)	0.090
12th	1096 (102.6-4854)	2162 (233-6014)	0.414
24th	397.4 (104.9-4820)	1609 (31-4842)	0.630

Legend: NGAL=neutrophil gelatinase-associated lipocalin; AKI=acute kidney injury; *Mann-Whitney test.

Table 4. AUC-ROC based on NGAL at 0th hour to predict AKI each grade

NGAL at 0th hour	AUC	p value
Predict AKI grades 1, 2, 3	0.715 (0.528-0.902)	0.047
Predict AKI grades 2, 3	0.816 (0.650-0.982)	0.028
Predict AKI grade 3	0.924 (0.829-1.000)	0.017

Legend: AUC=area under the curve; ROC=receiver operator characteristic; NGAL=neutrophil gelatinase-associated lipocalin; AKI=acute kidney injury.

Table 5. Sensitivity, specificity, PPV, NPV, LR, McNemar, Kappa, and AUC on NGAL cut-off of every level of AKI

Parameter	Result		
	AKI grades 1-3	AKI grades 2-3	AKI grade 3
Cut-off (ng/ml)	1242	3361	3834
Sensitivity (%)	76.5	80	100
Specificity (%)	61.5	72	89
PPV (%)	72.2	36.4	50
NPV (%)	66.7	94.7	100
LR (p)	4.507 (0.034)	4.778 (0.029)	11.187 (0.001)
Mc Nemar test (p)	1.000	0.070	0.250
Kappa (p)	0.384 (0.035)	0.351 (0.028)	0.615 (<0.001)
AUC	0.715 (0.528-0.902)	0.816 (0.650-0.982)	0.924 (0.829-1.000)

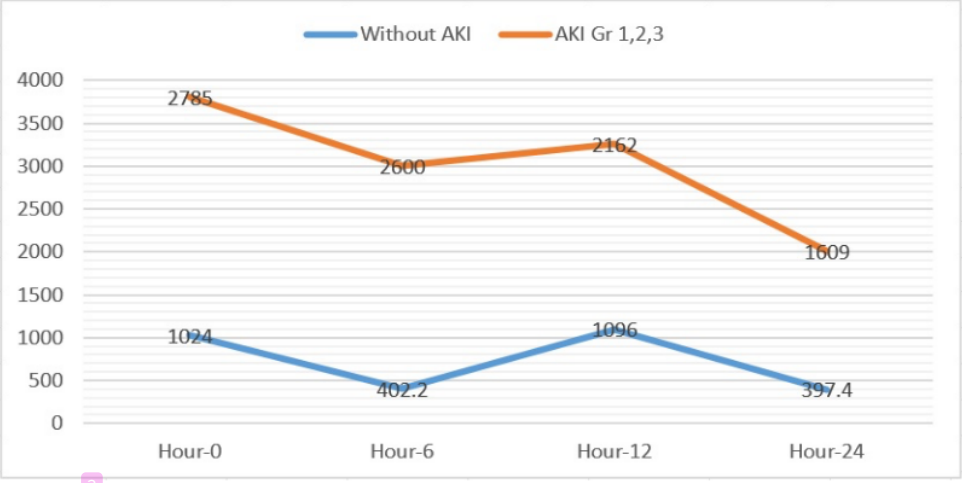
Legend: PPV=positive predictive value; NPV=negative predictive value; LR=likelihood ratio; AUC=area under the curve; NGAL=neutrophil gelatinase-associated lipocalin; AKI=acute kidney injury.

Table 6. Comparison of the sensitivity, specificity, PPV, NPV, and AUC with other study

Parameter	AKI grades 1, 2, 3		
	This study	Lawang, et al, 2014 (29)	Wai, et al, 2013 (28)
NGAL cut-off	1242 ng/ml	1447.01 ng/ml	1544 ng/mg uCr
Patient type	Pediatric sepsis	Pediatric sepsis	Critically ill
AKI diagnosis criteria	KDIGO	RIFLE	Not mentioned
Sensitivity (%)	76.5	100	84
Specificity (%)	61.5	63	80
PPV (%)	72.2	27.27	Not mentioned
NPV (%)	66.7	100	Not mentioned
AUC	0.715	0.826	0.82

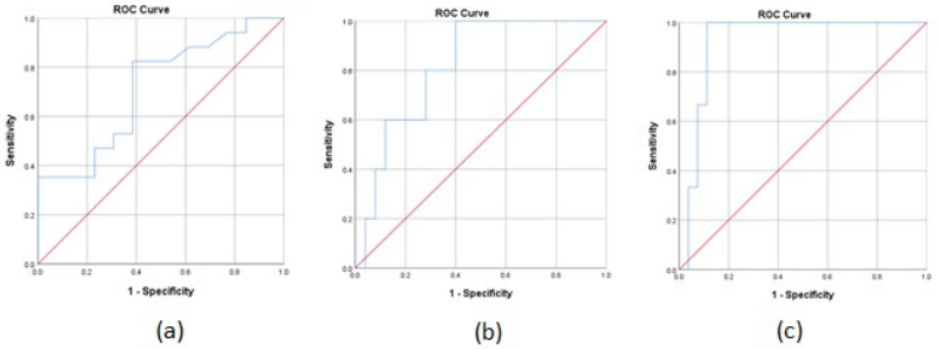
Legend: PPV=positive predictive value; NPV=negative predictive value; AUC=area under the curve; AKI=acute kidney injury; KDIGO=Kidney Disease: Improving Global Outcomes; RIFLE=Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; uCr=urinary creatinine.

Figure 1. Comparison chart of median urinary NGAL values at 0, 6, 12, and 24 hours between pediatric septic patients with AKI and without AKI



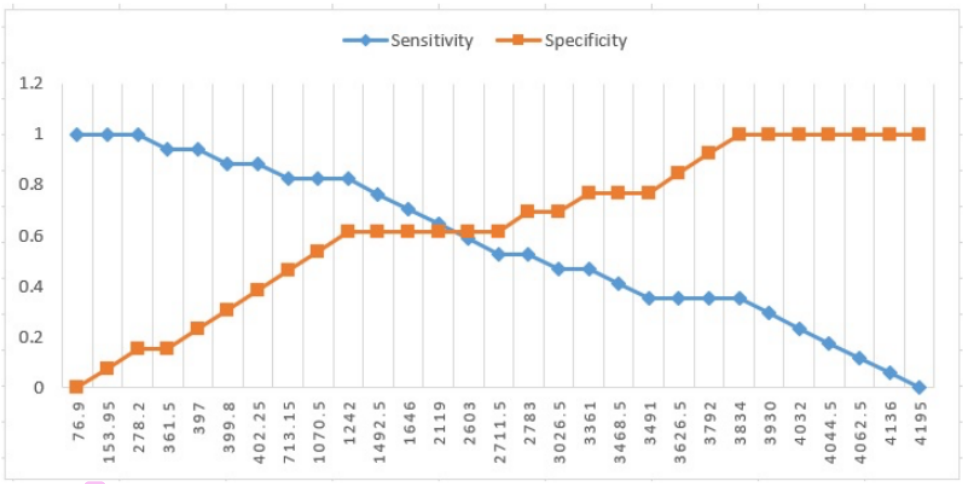
Legend: NGAL=neutrophil gelatinase-associated lipocalin; AKI=acute kidney injury.

Figure 2. ROC curve illustrating NGAL value at 0th hour to the incidence of (a) AKI grades 1-3, (b) AKI grades 2-3, and (c) AKI grade 3 only, based on KDIGO criteria



Legend: ROC=receiver operator characteristic; NGAL=neutrophil gelatinase-associated lipocalin; AKI=acute kidney injury; KDIGO=Kidney Disease: Improving Global Outcomes; AUC=area under the curve.

Figure 3. Cut-off point graph explaining the relationship between 0th hour NGAL urine and AKI grades 1, 2, and 3



Legend: NGAL=neutrophil gelatinase-associated lipocalin; AKI=acute kidney injury.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11