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Research Article

# Possible Role of Interleukin-18 in Early Prediction of Acute Kidney Injury in Critically Ill Patients

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## Abstract

**Background:** Acute kidney injury (AKI) is associated with increased mortality, length of hospital stay and cost. But the onset of AKI is often not recognized. The recent development of novel biomarkers for the prediction and early detection of AKI promises to be a real advance in critical care and acute nephrology. Interleukin-18 (IL-18) has been suggested to be a sensitive and specific biomarker for acute kidney injury (AKI). With the evidence accumulating, contradictory results have raised concerns about the predictive value of AKI across various settings.

**Materials and Methods:** It was a prospective cohort study on the newly admitted patients to the Intensive care unit. IL-18 was measured on first day of admission (day 0) and after 48 hours (day 2). We evaluated the association of IL-18 with developing new AKI, the need for renal replacement therapy (RRT) and 30-day mortality. We calculated areas under receiver operating characteristics curves (AUCs), best cut-off values. We also measured serum neutrophil gelatinase-associated lipocalin (NGAL) on the day of admission (day 0) and (day 2) and compared it to the predictive and diagnostic value of IL-18 in urine.

**Results:** The results showed the IL-18 readings were much higher in the patients who developed AKI on both day 0 and day 2. The area under the curve (AUC) for (day 0) was reported to be 0.681. The sensitivity and specificity for prediction of AKI were 72 and 65% respectively. While the AUC for (day 2) was 0.809, with sensitivity and specificity of 85% and 88% respectively. IL-18 predicted the need for RRT with an AUC 0.7 (day 0); sensitivity and specificity were 68% and 69% respectively. The AUC for (day 2) was 0.82, while the sensitivity and specificity were 82% and 83% respectively. Regarding the prediction of mortality, the AUC for the first reading (day 0) was 0.678; the sensitivity and specificity were 64% and 72% respectively. While the AUC for second reading (day 2) was 0.75, with sensitivity and specificity of 70% and 76% respectively.

**Conclusion:** Multiple readings of Interleukin-18 in urine (IL-18) can be a useful marker for early detection of AKI in critically ill patients, in addition for prediction of the complications including the need for RRT and mortality.

***Keywords:*** *Acute Kidney Injury (AKI); Acute Renal Failure (ARF); Interleukin-18 (IL-18)*

## Introduction

Acute kidney injury (AKI) represents an acute decline in renal function that leads to structural changes [1]. AKI is considered the correct nomenclature for the clinical disorder formerly termed "acute renal failure" (ARF). Although it is a common clinical problem with high implications, the detection of AKI is often delayed [2]. Despite several advances in the understanding and the pathogenesis and treatment of AKI. Five percent of hospital admissions and 30% of ICU admissions carry the diagnosis of AKI. Hospital mortality for patients with AKI has been reported to vary from 28% - 60% [3].

The loss of kidney function that defines AKI is most commonly detected by measurement of the serum creatinine, which is used to estimate the glomerular filtration rate (GFR) [4]. Several problems are associated with the use of serum creatinine to quantitatively define AKI: First serum creatinine does not accurately reflect the GFR in a patient in whom it is not in steady state. In the early stages of AKI, the serum creatinine may be low, even though the actual (not estimated) GFR is markedly reduced, since there may not have been sufficient time for the creatinine to accumulate [5]. Second creatinine is removed by dialysis; as a result, it is usually not possible to assess kidney function by measuring the serum creatinine once dialysis is initiated [5]. Third numerous epidemiologic studies and clinical trials have used different cut-off values for serum creatinine to quantitatively define AKI [6].

### *Novel markers of prediction and early diagnosis of AKI

The ability of biomarkers to predict AKI has been studied intensely in several different clinical settings. For a sound interpretation of the reported results, it is important to realize that the studies present a mixture of "AKI diagnosis confirmation" in patients with established AKI and "AKI early prediction" in patients with developing AKI. Obviously, these are two different entities with different clinical impacts. For the clinical application of a new biomarker, it should proved to be more accurate with earlier detectability than the current gold standard serum creatinine [7].

Interleukin-18 (IL-18) is a pro-inflammatory protein that acts as an immune-regulatory agent. It has been associated with many autoimmune diseases, ischemic heart disease, emphysema, metabolic syndrome and sepsis [8]. Regarding AKI, studies first showed that IL-18 mediates tubular injury in mice predisposed to ischemia, and that the lack of IL-18 protects from tubular damage. Thereafter, data from humans indicated that urine IL-18 levels are higher in patients with kidney injury compared either with patients with transient functional renal dysfunction or with healthy controls. Based on pathophysiological plausibility urine IL-18 has been suggested as a new biomarker for AKI [9].

A candidate biomarker for renal parenchymal injury, the cytokine IL-18 is formed in the proximal tubules and can be detected in the urine [8]. Parikh., *et al*. [9] determined that patients with ATN had significantly higher levels of IL-18 in their urine than did control subjects or persons with other forms of kidney disease. In renal transplant recipients, those patients with delayed graft function during the immediate post-transplantation period had higher urinary levels of IL- 18 than did patients who had immediate graft function. Furthermore, patients with ischemia-reperfusion injury, glycerol injection, and cisplatin-induced renal injury have likewise been noted to have elevated levels of this pro-inflammatory cytokines [10].

NGAL is a 25-kD protein of the lipocalin family. Elevation of NGAL levels has been documented in the plasma and urine of animal models of ischemic and nephrotoxic acute kidney injury; hence, NGAL is considered to be a novel urinary biomarker for ischemic injury [11]. In human studies, the expression of the NGAL messenger ribonucleic acid (mRNA) and protein has been shown to be significantly increased in the kidney tubules in the following settings: Ischemic, septic, or post-transplantation AKI [12]. Within 2 - 6 hours after cardiopulmonary bypass surgery [13]. At frequent intervals for 24 hours post-cardiopulmonary bypass surgery in children [12]. Following contrast administration [14]. NGAL has been thought to reduce injury by inhibiting apoptosis and increasing the normal proliferation of kidney tubule cells. More specifically, NGAL has been reported to up-regulate heme- oxygenase-1, which preserves proximal tubule N-cadherin,

and subsequently inhibits cell death [15]. Moreover, NGAL has shown some potential to aid in the diagnosis of early acute tubular necrosis (ATN) and differentiate it from pre-renal disease [14].

## Patients and Methods

The calculated sample size was 75 patients, so we decided to recruit 90 patients in this study to prevent bias.

**Inclusion criteria:** 1. Patients above 18 years old, 2. Critical ill patients admitted primarily to intensive care units of Alexandria university hospitals, 3. Length of stay more than 48 hours.

**Exclusion criteria:** 1. Patients with end stage renal disease and/or on maintenance hemodialysis, 2. Readmitted patients who received Renal replacement therapy (RRT) during their previous admission, 3. Organ donors, 4. Organ recipients of Kidney transplantation, 5. Anuric patients on the day of admission, 6. AKIN score of ≥ 2.

All patients included in the study were subjected to the following:

1. Thorough history taking.
2. Full clinical examination.
3. APACHE (Acute physiology and chronic health evaluation) II score was applied to all patients on the day of admission to ICU (day 0).
4. Assessment of the renal condition using AKIN criteria.
5. Laboratory investigation:

    a) Urine IL-18 measurement using ELISA Quantitative technique on the day of admission (day 0) and (day 2). Urine IL-18 measurement using ELISA Quantitative technique on the day of admission (day 0) and (day 2). Urine samples were aseptically collected in sterile container from all eligible patients on admission and 48 hours later. Samples were centrifuged to remove particulate matter, then aliquoted and stored till assayed at -80°C. We collected urine samples from all eligible patients on admission and 48 hours later. We aliquoted and stored the samples at -80°C. We used the (IAab Human Interleukin-18 ELISA Kit Catalog No: E0064h, China) for analyses. For IL-18, the measurable range was 15.6 -1000 pg/ul.

    **Test principle:** The microtiter plate provided in this kit has been pre-coated with an antibody specific to IL-18. Standards or samples were then added to the appropriate microtiter plate wells with a biotin conjugated polyclonal antibody preparation specific for IL-18 and Avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. Then a TMB substrate solution was added to each well. Only those wells that contain IL-18, biotin-conjugated antibody and enzyme-conjugated Avidin would exhibit a change in color. The enzyme-substrate reaction was terminated by the addition of a sulphuric acid solution and the color change was measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of IL-18 in the samples was then determined by comparing the O.D. of the samples to the standard curve.

    b) Serum neutrophil gelatinase-associated lipocalin (NGAL) on the day of admission (day 0) and (day 2). Serum Neutrophil gelatinase-associated lipocalin (NGAL) on the day of admission (day 0) and (day 2) using Enzyme Linked ImmunoSorbent Assay (ELISA) for the Quantitative Measurement of Human Neutrophil Gelatinase-Associated Lipocalin (NGAL) Levels (Epitope diagnostics, USA) reference number (KTR -833). The samples were collected by aspirating 3 mls of blood in red capped vacutainer tubes and stored after separation at - 20°C.

**Test principle:** This ELISA kit was designed, developed and produced for the quantitative measurement of human NGAL in serum samples. The assay utilized the "sandwich" technique with selected antibodies that bind to various epitopes of NGAL. Assay standards, controls and patient samples were added directly to wells of a microtiter plate that was coated with antibody to human NGAL and incubated at room temperature for one hour. The plate was then washed and horseradish peroxidase (HRP) conjugated anti NGAL was added to each well. After an additional incubation period, a "sandwich" of solid-phase polyclonal antibody - human NGAL - HRP-conjugated antibody" was formed. The unbound antibodies and buffer matrix were removed in the subsequent washing step. For the detection of this immune-complex, the well was then incubated with a substrate solution in a timed reaction, which is terminated with an acidic reagent (i.e. ELISA stop solution). The absorbance was then measured in a spectrophotometric microplate reader. The enzymatic activity of the immune-complex bound to the wall of each microtiter well was directly proportional to the amount of human NGAL in the test sample. A standard curve was generated by plotting the absorbance versus the respective human NGAL concentration for each standard on a point-to-point or 4-parameter curve fitting. The concentration of human NGAL in test samples was determined directly from this standard curve. The normal high cut-off for NGAL concentration (according to the manufacturer) by using this ELISA was 500 ng/mL with an average level greater than 106 ng/mL (range 48 - 390 ng/mL, SD 56 ng/mL).

c) Serum Creatinine.

d) Creatinine clearance estimation using Cock-croft and Gault formula.

6. Follow up of the patients:

a) Serum creatinine every 48 hours.

b) Urine output every 24 hours.

c) Assessment of renal function using AKIN criteria daily.

7. The primary end point was the need for Renal Replacement Therapy (RRT) in 30 days and the secondary end point was 30 days mortality.

## Results

The calculated sample size was 75 patients, so we decided to recruit 90 patients in this study to prevent bias. All subjects included in the study were subjected to history taking, clinical examination, laboratory investigation, radiological assessment and follow up of the patients.

Table 1 shows the comparison between AKI and non AKI regarding basic characteristic and clinical data, it was found that there was a significant difference between AKI and non AKI regarding age, weight and clinical findings, cause of mortality, APACHE II, creatinine and UOP at base line.

| | Non AKI "n = 35" | | AKI "n = 55" | | P |
|---|---|---|---|---|---|
| **Age** | | | | | |
| Range | 20.00 - 85.00 | | 21.00 - 88.00 | | 0.002* |
| Mean ± S.D. | 46.29 ± 20.09 | | 58.31 ± 14.83 | | |
| **Gender** | | | | | |
| Male | 20 | 57.1% | 34 | 54.0% | 0.412 |
| Female | 15 | 42.9% | 21 | 36.0% | |

| | | | | | |
|---|---|---|---|---|---|
| Weight<br>Range Mean ± S.D. | 55.00 - 90.00<br>68.57 ± 11.09 | | 50.00 - 120.00<br>76.62 ± 14.01 | | 0.005* |
| **Clinical findings** | | | | | |
| CKD | 0 | 0.0 | 22 | 40.0 | 0.001* |
| HTN | 12 | 34.3 | 37 | 67.3 | 0.002* |
| DM | 9 | 25.7 | 27 | 49.1 | 0.023* |
| Cardiac | 11 | 31.4 | 21 | 38.2 | 0.337 |
| COPD | 7 | 20.0 | 6 | 10.9 | 0.186 |
| Obesity | 4 | 11.4 | 13 | 23.6 | 0.121 |
| Immuno-compromised | 7 | 20.0 | 12 | 21.8 | 0.528 |
| **Cause mortality** | | | | | |
| ARDS | 4 | 11.4 | 3 | 5.5 | 33.904<br>0.0001* |
| Bleeding | 0 | 0.0 | 1 | 1.8 | |
| Cardiogenic Shock | 0 | 0.0 | 4 | 7.3 | |
| Brain Herniation | 2 | 5.7 | 1 | 1.8 | |
| Septic shock | 0 | 0.0 | 22 | 40.0 | |
| **Apache II**<br>Range<br>Mean ± S.D. | 4.00 - 33.00<br>17.14 ± 6.61 | | 6.00 - 32.00<br>21.60 ± 5.91 | | 0.0001* |
| **Creatinine (base line)**<br>Range (mg/dl)<br>Mean ± S.D. | 0.30 - 1.30<br>0.76 ± 0.27 | | 0.37 - 3.20<br>1.48 ± 0.72 | | 0.0001* |
| **UOP (base line)**<br>Range (cc/hr)<br>Mean ± S.D. | .50 - 2.00<br>1.18 ± 0.51 | | .30 - 2.00<br>0.73 ± 0.38 | | 0.0001* |

***Table 1:*** *Comparison between AKI and non AKI regarding demographic data.*

Table 2 shows comparison between AKI and non AKI regarding readings at day (0) and day (2) of IL-18 and NGAL. There was statistical significant increase in AKI group than non AKI group regarding 1st and 2nd readings of IL-18 and NGAL ($P < 0.05$).

| | **Non AKI**<br>**"n = 35"** | **AKI**<br>**"n = 55"** | **P** |
|---|---|---|---|
| **IL-18 1st**<br>Range pg/ul<br>Mean ± S.D. | 3.10 - 610.00<br>106.04 ± 114.65 | 7.00 - 910.00<br>225.26 ± 207.95 | 0.003* |
| **IL-18 2nd**<br>Range pg/ul<br>Mean ± S.D. | 3.00 - 450.00<br>84.69 ± 113.48 | 1.00 - 1159.00<br>280.71 ± 272.25 | 0.0001* |
| **Diff. IL-18**<br>Range pg/ul<br>Mean ± S.D. | -182 to 207<br>-21.01 ± 73.568 | -263 to 741<br>54.90 ± 177.778 | 0.019* |

| | | | |
|---|---|---|---|
| **NGAL 1st** | | | |
| Range ng/mL | 53.00 - 500.00 | 20.00 - 500.00 | 0.020* |
| Mean ± S.D. | 182.83 ± 120.95 | 246.80 ± 126.87 | |
| **NGAL 2nd** | | | |
| Range ng/mL | 46.00 - 488.00 | 51.00 - 497.00 | 0.001* |
| Mean ± S.D. | 149.37 ± 110.19 | 247.33 ± 151.54 | |
| **Diff. NGAL** | | | |
| Range ng/mL | -199.0 to 169.0 | -310 to 324.00 | 0.470 |
| Mean ± S.D. | -1.83 ± 87.61 | -16.96 ± 101.64 | |

***Table 2:*** *Comparison between AKI and non AKI regarding 1st and 2nd readings of IL-18 and NGAL.*

**Significant at level 0.05.*

Table 3 shows multivariable logistic regression models for different risk factors which affect morality, the most significant risk factors were age, IL-18 at day (2), change of IL-18 between both readings (days 0 and 2), NGAL at days 0 and 2, MAP on admission, and APACHE II score on admission.

| Factors | O.R. | C.I | P |
|---|---|---|---|
| Age | 2.01 | 0.23 - 0.82 | 0.001* |
| IL-18 (1st) | 1.11 | 0.31 - 1.32 | 0.107 |
| IL-18 (2nd) | 1.98 | 0.33 - 0.68 | 0.013* |
| Change of IL-18 | 2.33 | 0.10 - 0.89 | 0.001* |
| NGAL (1st) | 1.75 | 0.24 - 0.72 | 0.0068* |
| NGAL (2nd) | 1.93 | 0.31 - 0.70 | 0.005* |
| Creat. (Base line) | 0.823 | 0.25 - 1.25 | 0.236 |
| Cr. Cl. (Base line) | 0.911 | 0.39 - 2.04 | 0.421 |
| UOP (Base line) | 1.00 | 0.28 - 2.16 | 0.365 |
| MAP on admission | 1.75 | 0.36 - 0.89 | 0.042* |
| Apache II | 3.12 | 0.16 - 0.75 | 0.002* |

***Table 3:*** *Different risk factors relation with morality.*

Table 4 shows the readings of IL-18 and NGAL at day 0 in diagnosis of AKI. IL-18 (1st) has cut off value 180 pg/ul, sensitivity 72%, specificity 65% and accuracy 70%. NGAL (1st) has cut off value 220 ng/mL, sensitivity 65, specificity 60% and accuracy 62%, while IL-18*NGAL has cut off value 39600, sensitivity 70.2%, specificity 64% and accuracy 69%. The readings of IL-8 and NGAL at day 2 in diagnosis of AKI. IL-18 (2nd) has cut off value 185 pg/ul, sensitivity 85%, specificity 88% and accuracy 86%. NGAL (2nd) has cut off value 205 ng/mL, sensitivity 72, specificity 75% and accuracy 73.0%, while IL-18*NGAL has cut off value 37925, sensitivity 84.0%, specificity 86% and accuracy 85%.

| Test Result Variable(s) | Area | p-value | Cut off value | Sensitivity | Specificity | Accuracy |
|---|---|---|---|---|---|---|
| IL 18 (1st) | .681 | .004 | 180 | 72.0 | 65.0 | 70.0 |
| NGAL (1st) | .666 | .008 | 220 | 65.0 | 60.0 | 62.0 |
| IL-18*NGAL | .692 | .002 | 39600 | 70.2 | 64.0 | 69.0 |
| **2nd day** | | | | | | |
| IL-18 (2nd) | .809 | .0001 | 185 | 85.0 | 88.0 | 86.0 |
| NGAL (2nd) | .697 | .002 | 205 | 72.0 | 75.0 | 73.0 |
| IL-18*NGAL | .805 | .0001 | 37925 | 84.0 | 86.0 | 85.0 |

***Table 4:*** *IL-18 and NGAL at day 0 and 2 in diagnosis of AKI.*

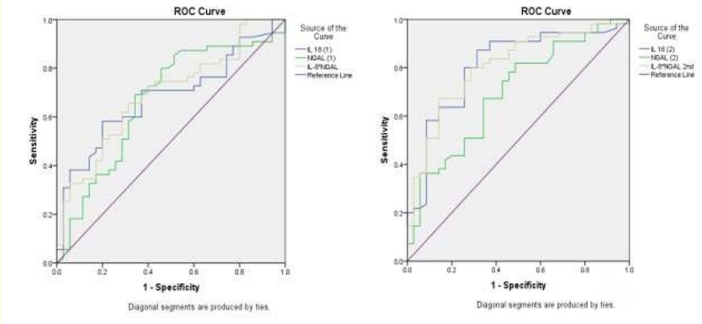


***Figure 1:*** *Receiver operating characteristics curves (ROC AUC) of IL-18 and NGAL at days 0 and 2 as diagnostic factors of AKI.*

Table 5 shows the readings of IL-8 and NGAL at day 0 as predictors of RRT. IL-18 (1st) has cut off value 220 pg/ul, sensitivity 72%, specificity 68% and accuracy 69%. NGAL (1st) has cut off value 250 ng/mL, sensitivity 75, specificity 60% and accuracy 72.6%, while IL-18*NGAL has cut off value 55000, sensitivity 76.0%, specificity 72% and accuracy 74%. IL-18 and NGAL at day 2 as a prediction of RRT. IL-18 (2nd) has cut off value 270 pg/ul, sensitivity 85%, specificity 82% and accuracy 83%. NGAL (2nd) has cut off value 280 ng/mL, sensitivity 86, specificity 80% and accuracy 84.0%, while IL-18*NGAL has cut off value 75600, sensitivity 69.0%, specificity 66% and accuracy 67%.

| Test Result Variable(s) | Area | p-value | Cut off value | Sensitivity | Specificity | Accuracy |
|---|---|---|---|---|---|---|
| IL-18 (1st) | 0.701 | 0.002 | 220 | 72.0 | 68.0 | 69.0 |
| NGAL (1st) | 0.708 | 0.001 | 250 | 75.0 | 70.0 | 72.6 |
| IL-18* NGAL | 0.722 | 0.001 | 55000 | 76.0 | 72.0 | 74.0 |
| **2nd day** | | | | | | |
| IL-18 (2nd) | 0.827 | 0.0001 | 270 | 85.0 | 82.0 | 83.0 |
| NGAL (2nd) | 0.828 | 0.0001 | 280 | 86.0 | 80.0 | 84.0 |
| IL-18* NGAL | 0.642 | 0.029 | 75600 | 69.0 | 66.0 | 67.0 |

***Table 5:*** *IL-18 and NGAL at days 0 and 2 of RRT.*

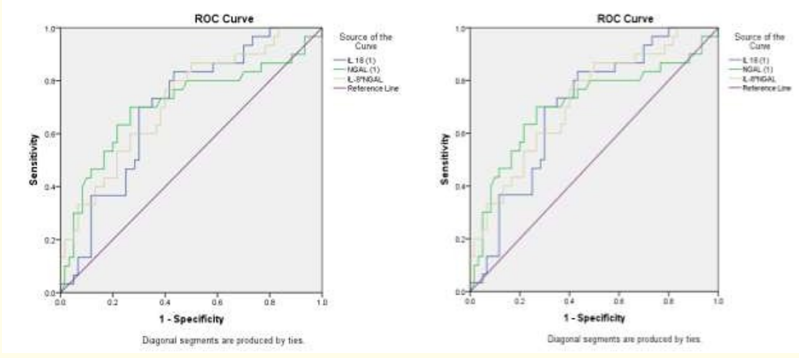


***Figure 2:*** *Receiver operating characteristics curves (ROC AUC) of IL-18 and NGAL at days 0 and 2 in prediction of RRT.*

Table 6 shows IL-18 and NGAL at day 0 as predictors of mortality. IL-18 (1st) has cut off value 185 pg/ul, sensitivity 64%, specificity 72% and accuracy 67%. NGAL (1st) has cut off value 240 ng/mL, sensitivity 63, specificity 69% and accuracy 65.0%, while IL-18*NGAL has cut off value 44400, sensitivity 70.0%, specificity 66% and accuracy 69%. NGAL at day 2 as a prediction of mortality. IL-18 (2nd) has cut off value 265 pg/ul, sensitivity 79.8%, specificity 70% and accuracy 76%. NGAL (2nd) has cut off value 275 ng/mL, sensitivity 82, specificity 75% and accuracy 80.0%, while IL-18* NGAL has cut off value 72875, sensitivity 68.0%, specificity 72% and accuracy 70%.

| Test Result Variable(s) | Area | p-value | Cut off value | Sensitivity | Specificity | Accuracy |
|---|---|---|---|---|---|---|
| IL-18 (1st) | 0.678 | 0.004 | 185 | 64.0 | 72.0 | 67.0 |
| NGAL (1st) | 0.669 | 0.007 | 240 | 63.0 | 69.0 | 65.0 |
| IL-18*NGAL | 0.682 | 0.004 | 44400 | 70.0 | 66.0 | 69.0 |
| **2nd day** | | | | | | |
| IL-18 (2nd) | .753 | .0001 | 265 | 79.8 | 70.0 | 76.0 |
| NGAL (2nd) | .809 | .0001 | 275 | 82.0 | 75.0 | 80.0 |
| IL-18*NGAL | .645 | .021 | 72875 | 68.0 | 72.0 | 70.0 |

***Table 6:*** *IL-18 and NGAL at days 0 and 2 in prediction of mortality.*

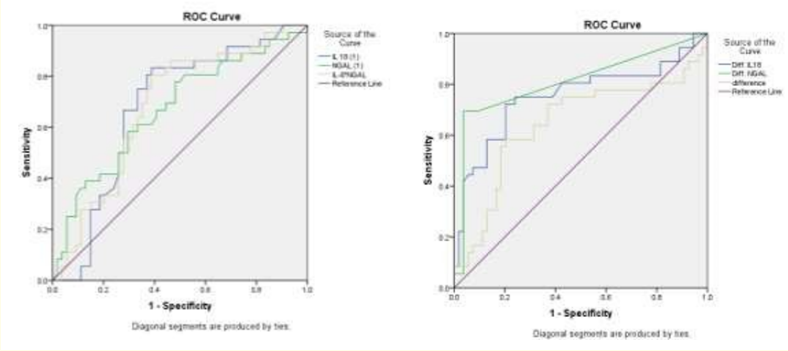


***Figure 3:*** *Receiver operating characteristics curves (ROC AUC) of IL-18 and NGAL at days 0 and 2 as predictors of mortality.*

## Discussion

Acute kidney injury (AKI) is a common condition associated with a worse outcome in critically ill patients. Although regarded as the standard indicators of kidney function loss, serum creatinine (sCr) level and urine output are recognized as having limitations [16]. On one hand, sCr cannot accurately reflect the glomerular filtration rate (GFR) in a patient with unsteady state, and urine output is easily affected by water intake and the primary water load of the body. On the other hand, sCr and urine output have limited sensitivity and specificity, and a delayed response to kidney impairment. All these factors suggest that sCr and urine output are not appropriate markers in the early detection of AKI. Thus, an accurate and timely biomarker to predict AKI onset or progression after renal insult is urgently needed [17].

In contrast to creatinine, Interleukin-18 (IL-18) is a proinflammatory cytokine that is released in response to injury to the renal tubules. It is a member of the IL-1 family of cytokines, is synthesized as an inactive 23-kDa precursor by several tissues including monocytes, macrophages, and proximal tubular epithelial cells and is processed into an active 18.3 kDa cytokine by caspase-1. It has been demon-

strated in some animal studies as a mediator of renal ischemia-reperfusion injury, inducing acute tubular necrosis, and neutrophil and monocyte infiltration of the renal parenchyma. More recently, numerous clinical studies have focused on the diagnostic accuracy of IL-18 level in predicting AKI [18,19].

This was a prospective cohort study which took place between first of February 2017 and concluded on 15th of May 2017. The study was conducted on all newly admitted critically ill patients who were admitted in critical care units of Alexandria university hospitals and fulfilled the inclusion criteria mentioned earlier in the materials and methods in a trial to evaluate the value of IL-18 in prediction, early detection and determination of the prognosis of AKI in critical ill patients.

We used the AKIN (Acute kidney injury network) score guidelines with both daily creatinine (Cr) and hourly urine output measurements to define AKI. We defined progression of AKI as worsening of AKIN stage or new onset of AKI during the ICU stay [7,16].

The comorbidities' results in this study found that majority of patients in the AKI group were hypertensives, diabetics and/or CKD patients which were similar to the findings of Nisula., *et al*. [19] and Endre., *et al*. [21] with special concern that the main association in both studies were Diabetes Mellitus while Hypertensives percentage in our study were more in addition that CKD percentage was higher than any other study we encountered during our review which points the impact of those 2 diseases in our community.

Regarding the IL-18 readings were much higher in the patients who developed AKI, and the significant difference at day 2 was much more profound and that was same finding encountered by Lin., *et al*. [22] in their meta-analysis which involved more than eleven studies from USA, China, and Australia. They found significant differences between readings of the first 12, 24 and 48 hours in the studies done in critical care areas whether cardiothoracic, general or coronary ICUs, while in the studies done in the medical wards, there were no significant difference between subsequent readings, and those findings can be easily explained by the aggressive criteria of the critical illness and/or the inflammatory responses which are more common in the ICU patients as IL-18 itself is an inflammatory marker. Nisula., *et al*. [19] in their multicentered study which is considered the largest trial on critically ill patients so far found increased association with AKI but they measured it only twice in the first 24 hours and took the highest reading (IL-18 max) and the difference between both readings, IL-18 was shown to peak early (0 - 24h) after an insult to the kidneys.

According to our study, AUC for the first reading of IL-18 (day 0) was reported to be 0.681. Nisula., *et al*. [19] reported an AUC of 0.586 for IL-18 in prediction of AKI developing during the next 48h after the day of admission. Four studies by Doi., *et al*. [20], Endre., *et al*. [21], Siew., *et al*. [23], Parikh., *et al*. [9] and by Metziger., *et al*. [24] have previously reported the association of IL-18 to new AKI in critically ill adult patients, four of these studies with AUCs from 0.55 to 0.62. The study by Parikh., *et al*. [9] which comprised 138 lung injury patients, presented the most encouraging AUC of 0.73 for IL-18 in prediction of AKI. One of the largest studies of IL-18 in an ICU population which was done by Endre., *et al*. [21] (comprising 528 patients) presented poor results (AUC 0.55) even though the development of AKI was observed for 7 days.

The sensitivity and specificity for the first reading in diagnosis of AKI were 72 and 65% respectively. Liu., *et al*. [25] analyzed data from 18 studies from 7 countries in their meta-analysis. Across all settings, the diagnostic odds ratio (DOR) for urinary IL-18 level to predict AKI was 4.22 (95% CI, 2.90 - 6.14), with sensitivity and specificity of 0.58 and 0.75, respectively. The area under the receiver operating characteristic curve (AUC) of urinary IL-18 level to predict AKI was 0.70 (95% CI, 0.66 - 0.74). Subgroup analysis showed the DOR/AUC of urinary IL-18 was 5.32 (95% CI, 2.92 - 9.70)/0.72 (95% CI, 0.68 - 0.76) in cardiac surgery patients and 3.65 (95% CI, 1.88 - 7.10)/0.66 (95% CI, 0.62 - 0.70) in intensive care unit or coronary care unit patients.

The Interleukin18 (IL-18) readings on day 0 in our study showed increased association with the need for RRT in the first 30 days after admission with an AUC of 0.7. Sensitivity and specificity were 68 and 70% respectively. Nisula., *et al*. [19] found that there was also association with the RRT but they suspected the usefulness of this marker in prediction of RRT, the difference between our study and that of

Nisula., *et al*. [19] that their endpoint was the occurrence of AKI and/or RRT in the first 3 days after admission. In addition, as mentioned before they measured IL-18 twice on admission and after 24 and then studied the relation of the maximum readings (IL-18max), the difference between both readings to the RRT need. In their study IL-18max predicted RRT with an AUC (95% CI) of 0.655 (0.572 - 0.739), and the change in IL-18 with an AUC (95% CI) of 0.531 (0.428 - 0.633). Zheng., *et al*. [26] also reported moderate prediction of dialysis with IL-18 but they used also the ratio of IL-18/urine creatinine (ucr) in their study and their end-point was AKI within 7 days of admission but their patients' were children who underwent Cardiopulmonary bypass surgeries. Siew., *et al*. reported as well increased association of IL-18 with the need for dialysis within 28 days [23]. Endre., *et al*. [21] with an observation period of (19 days) reported an AUC of 0.73 for IL-18 in prediction of RRT, while Klein., *et al*. [27] in their meta-analysis found that IL-18 had an AUC of 0.668 (0.606 - 0.729) in the prediction of RRT need in patients with AKI and had a AUC of 0.668 (0.606 - 0.729) and if normalized to urinary creatinine had an AUC of 0.761 (0.661 - 0.862).

There was also increased association between IL-18 in day 0 and day 2 and the mortality in 30 days, AUC for the first day (day 0) was 0.68 and for the day 2 was 0.75. Sensitivity and specificity for the first reading were 64% and 72%, while were 79.8% and 70% for the second reading. Nisula., *et al*. [19] found that (IL-18) predicted 90-day mortality with an AUC (95% CI) of 0.536 (0.497 - 0.574), and the change in IL-18 with an AUC (95% CI) of 0.489 (0.447 - 0.532), while Endre., *et al*. [21] found an AUC of 0.68 in prediction of Mortality in 7 days. Siew., *et al*. [23] and Parikh., *et al*. in 2 studies [18,28] also found increased association between the IL-18 and mortality in 28 days.

The difference between the first reading (day 0) and the second reading (day 2) revealed significant difference regarding the development of AKI, RRT need and Mortality. These findings were also encountered by Nisula., *et al*. [19] but they studied it only the difference between both readings in the first 24 hours. Siew., *et al*. [18] and Endre., *et al*. [21] agreed about that subsequent readings of IL-18 were more sensitive in the prediction of AKI, RRT need and Mortality. Lin., *et al*. [22] also found in their meta-analysis that subsequent and follow-up of IL-18 levels in urine were only useful in the studies done on ICU population.

The cut values for IL-18 on day 0 were 180 pg/ml, 220 pg/ml, 185 pg/ml for prediction of AKI, RRT need and mortality respectively, while that for day 2 were 185 pg/ml, 270 pg/ml and 265 pg/ml. According to Lin., *et al*. [22] that there is no clear consensus about the appropriate cutoff level of IL-18 to predict AKI and different thresholds have been reported by different studies, so it might be necessary for each center using urine IL-18 level for early AKI diagnosis to define a specific reference range and cutoff value for each clinical setting due to different reagents used in addition to different clinical settings and the study population. The numerical cutoff values varied significantly in the literature between (36 - 1800) pg/ml with the highest ranges were observed in neonatal and pediatric ICUs [22].

Our study found that Urine IL-18 and serum NGAL have similar AUC, sensitivity and specificity on the day of admission for early detection of AKI, while the third day showed slight preference for IL-18 in the diagnosis of AKI, these findings were similar to those found by Parikh., *et al*. [27] regarding similarity between both markers on the prediction of AKI although they did their research on postoperative patients after cardiac surgeries.

Regarding predicting the need for RRT, we found both markers have similar AUC, sensitivity, and specificity whether on day 0 or day 2 which also agrees again with Parikh., *et al* [28]. Klein., *et al*. [27] in their meta-analysis found that both serum NGAL and urine-18 have similar sensitivity in prediction of RRT need although Serum NGAL was slightly more sensitive with AUC of 0.75 while IL-18 had an AUC of 0.66. They also stated that serum NGAL has more evidence based and research studies than any other novel marker.

For mortality, the only comparative study we encountered was that of Parikh's., *et al*. [27] which found also similar sensitivity between both Urine IL-18 and serum NGAL in predicting the mortality, while most of the other studies studied the relation between serum NGAL and serum IL-18 like Zhu., *et al*. [28] or urine NGAL and urine IL-18 like Nisula., *et al*. [19] and both of those studies showed higher sensitivity towards NGAL in predicting the Mortality. The large studies or meta-analyses which studied both markers individually were with

contradictory results with more evidence still supporting serum NGAL. While Endre., *et al*. [21] showed moderate sensitivity of IL-18 as a predictor of Mortality, Nisula., *et al*. [19] found it as a poor predictor and doubted its usefulness in determining the prognosis of AKI patients. The same applies to serum NGAL with much larger discrepancies although the current evidence still support the usage of NGAL to early detect the AKI and predict the prognosis and these findings were signified in the meta-analyses recently published by Klein., *et al*. [27] and Haase., *et al* [29]. Others like Aydoğdu M., *et al*. [30] suspected its usefulness in prediction of AKI and Mortality, as they found that urine NGAL and urine Cystatin C are much more sensitive.

Sepsis has been defined in our study according to the latest definition published by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [31]. Because IL-18 is a cytokine itself, most of the studies [32,33] which studied IL-18 in urine gave a special concern to the septic patients to determine if there would be any association or relation between both of them especially that serum IL-18 was found elevated in some studies which studied AKI in septic patients [34]. Some earlier studies like Siew., *et al*. [21] found this kind of relation in which excretion of IL-18 in septic patients with AKI is more than other AKI patients. However, we couldn't find a relation between both readings of IL-18 in day 0 and 2 and sepsis on admission which was also the same finding of Nisula., *et al*. [19] and Parikh., *et al* [18]. Those findings support the hypothesis that urine IL-18 excretion is usually independent from that of the serum levels of IL-18 as it is reflective of tubular injury mainly [14].

## Conclusion

Multiple readings of Interleukin-18 in urine (IL-18) can be a useful marker for early detection of AKI in critically ill patients, in addition for prediction of the complications including the need for RRT and mortality.

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