Sensitivity And Specificity Of Urine Interleukin-18 as an Early Biomarker For Acute Kidney Injury

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Abstract

Background
Incidence of AKI in intensive care unit patients reach 60-70%, and the mortality rate is about 60%. IL-18 is a pro-inflammatory cytokine which increased in endogenous inflammation process. Studies in human showed that IL-18 concentration increased prior to AKI. The aims of this research is to determine the sensitivity and specificity of Interleukin-18 urine examination as an early biomarker for acute kidney injury.

Methods
There’re total of 66 subjects who met the inclusion criteria. All the subject were checked for the IL-18 urine level with Cloud Clone kit and creatinine serum were also checked 48 hours after admission.

Results
The results showed in the cut-off point of 411.25 Pg/mL , urine IL-18 has a sensitivity of 54.3 % and specificity 83.9%, positive predictive value 79.17%, negative predictive value 61.9% and accuracy of 68.18%

Conclusions
IL-18 urine holds a promise as an early biomarker of AKI and more sensitive and specific as an early biomarker for AKI compared to creatinine serum.

Key words : Acute Kidney Injury, Interleukin-18, sensitivity, specificity

Background

Incidence of AKI in intensive care patients reaches 60-70%. Changes in serum creatinine values are not sensitive for early diagnose of AKI because serum creatinine takes 24-36 hours to increase after kidney damage occurs. IL-18 is a proinflammatory cytokine that will increase during
inflammatory process. IL-18 levels will increase significantly in patients who experience pre-renal azotemia, urinary tract infections, chronic renal insufficiency, and nephrotic syndrome. Research shows IL-18 concentrations will increase due to AKI.\textsuperscript{1-3}

According to Kidney Disease Improving Global Outcomes (KDIGO) 2012, AKI was defined as an increase in cCr to \( \geq 26.5 \, \mu\text{mol} / \text{L} \) within 48 hours, or \( \geq 1.5 \) times the initial value in 7 days. However, the guide uses urine output and sCr values as staging criteria. In addition, because CSR is influenced by many factors and has low sensitivity and specificity for its relationship with AKI, it is very important to determine other early AKI biomarkers that are more sensitive, specific, and significant. Biomarkers that can be used for early diagnosis of AKI are Cystatin C, IL-18 (Interleukin-18), KIM-1 (Kidney Injury Molecule-1), L-FABP (Liver Fatty Acid Binding Protein), and NGAL (Neutrophil Gelatinase Associated Lipocalin).\textsuperscript{4-6}

IL-18, known as an inflammatory mediator, is produced by renal tubular epithelium and interstitial macrophages. IL-18 plays an active role in various kidney diseases, such as injury due to reperfusion, transplant rejection, and urinary tract infections. Levels of IL-18 are very physiologically low and increase several-fold in patients who experience AKI. Increased urine IL-18 levels in AKI are partly derived from damaged tubules. In a cross-sectional study of humans, urine IL-18 levels increased significantly in patients with AKI compared with people with chronic, urinary tract infections, kidney disease, and nephrotic syndrome.\textsuperscript{7-10} Furthermore, urine IL-18 is easily measured through commercially available kits, and the tests are fast, reliable, accurate, and relatively inexpensive, thus facilitating practicality as a biomarker for patients with AKI.

**Methods**

This diagnostic test was carried out in the ICU, HCU and PI general hospital of Dr. Mohammad Hoesin Palembang in June until the number of samples was fulfilled. A total of 66 samples were obtained that met the inclusion criteria. All samples were examined for urine IL-18 levels using a Cloud Clone kit and serum creatinine values were examined 48 hours after the patient admitted. The results of the study will be analyzed using the Receiver Operating Characteristic (ROC) curve with SPSS® version 25 and MedCalc version 18.6.
Results

This diagnostic test study had been carried out in the ICU, HCU, and P1 general hospitals of Dr. Mohammad Hoesin Palembang began in June 2018 until August 2018 with the aim of knowing the value of sensitivity and specificity of IL-18 examination compared with serum creatinine examination.

The sample of the study was all patients who had just been treated in the ICU, HCU and P1 who met the inclusion and exclusion criteria. The number of samples was 66 samples that met the study inclusion and exclusion criteria. As long as the research continues until completion, no sample withdraws or drops out.

From the results of the study it was found that out of 66 samples, 39 (59.1%) were male and 27 (40.9%) were female from 66 samples, the average age was 50.32 ± 16.591 with a median age of 50 years. The average age of the male subjects was 52.62 ± 17.75 with a median age of 58 years. The average age of female subjects was 47 ± 14.43 and the median age was 49 years.

Of the 66 samples, the majority of respondents were diagnosed with Cerebro Vascular Disease (CVD), which were 15 people (22.7%) followed by obstetrics, intracranial space occupying lession and post digestive surgery patient with 8 subjects each (12.1%).

There were 30 people (45.5%) diagnosed with Non-AKI, and 36 subjects (54.5%) experiencing AKI where 22 subjects with a diagnosis of AKI stage 1 (33.3%), subjects with a diagnosis of AKI stage 2 as many as 6 subjects (9.1%) and subjects with a diagnosis of AKI stage 3 were 8 subjects (12.1%).

There were 17 samples (77.27%) that had positive values both from the results of IL-18 and serum creatinine and as many as 26 samples (59.1%) which had negative values from both examinations. Diagnostic test results in sensitivity, specificity, accuracy, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, likelihood ratio test, AUC (Area Under Curve), and reliability test. Analysis of the results using the ROC curve with SPSS version 25.0 software (IBM Corporation and Others, NY, USA) and Epicale and MedCalc version 18.6 (MedCalc Software, Mariakerke, Belgium). The sensitivity in this study was 48.6% and the specificity in this study was 83.9% which means that IL-18 levels can specifically describe the diagnosis of AKI but are less sensitive.
The average value of sample serum creatinine was 2.03 mg/dL with an average value of male serum creatinine level of 1.26 mg/dL and the average value of serum sample creatinine in women was 2.56 mg/dL. From the group of patients with AKI, the mean serum creatinine level was 3.16 mg/dL compared with the group of non-AKI patients with an average serum creatinine level of 0.67 mg/dL and the mean serum creatinine level of patients with AKI stage 1 was 1.2 mg/dL, patients with AKI stage 2 was 2.1 mg/dL, patients with AKI stage 3 were 9.2 mg/dL.

**Table 1. Diagnostic Value of IL-18 Urine Examination**

<table>
<thead>
<tr>
<th>No</th>
<th>Diagnostic Value</th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sensitivitas (Sn)</td>
<td>48.6%</td>
<td>31.38% - 66.01%</td>
</tr>
<tr>
<td>2</td>
<td>Spesifisitas (Sp)</td>
<td>83.9%</td>
<td>66.27% - 94.55%</td>
</tr>
<tr>
<td>3</td>
<td>Accuracy</td>
<td>65.15%</td>
<td>52.42% - 76.47%</td>
</tr>
<tr>
<td>4</td>
<td>Positive predictive value (PPV)</td>
<td>77.27%</td>
<td>1.26 - 7.20</td>
</tr>
<tr>
<td>5</td>
<td>Negative predictive value (NPV)</td>
<td>59.09%</td>
<td>0.43 - 0.88</td>
</tr>
<tr>
<td>6</td>
<td>Prevalence</td>
<td>53.03%</td>
<td>40.34% - 65.44%</td>
</tr>
<tr>
<td>7</td>
<td>Likelihood ratio positive (LR+)</td>
<td>3.01</td>
<td>1.26 - 7.20</td>
</tr>
<tr>
<td>8</td>
<td>Likelihood ratio negative (LR-)</td>
<td>0.61</td>
<td>0.43 - 0.88</td>
</tr>
<tr>
<td>9</td>
<td>Area under curve (AUC)</td>
<td>0.642</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Reliability Test</td>
<td>0.567</td>
<td>-</td>
</tr>
</tbody>
</table>

The mean value of urine IL-18 levels in the sample was 378.48 Pg/mL with a mean urine IL-18 level of a male sample was 389.1 pg/mL and mean urine IL-18 level of a female sample was 363.0 Pg/mL. From the group of patients with AKI, the mean value of urine IL-18 levels was 409.28 Pg/mL compared with the group of non AKI patients with an average value of urine IL-18 levels of 341.5 Pg/mL. The average value of IL-18 levels the urine of patients with AKI stage 1 was 422.5 Pg/mL, patients with AKI stage 2 were 431.1 Pg/mL, patients with stage3 AKI were 356.5 Pg/mL.
DISCUSSION

AKI is an independent predictor of mortality and length of hospital stay. Severe cases require expensive therapy which slows down therapy which will worsen kidney damage and increase the need of human and financial resources. In 2012, Kidney Disease Improving Global Outcomes (KDIGO) issued a new classification that combines RIFLE and AKIN criteria. KDIGO also defines AKI as an increase in serum creatinine 0.3 mg / dL or more for 48 hours, or an increase in serum creatinine 1.5 mg / dL or more in the last 7 days, or urine output <0.5 mL / kg / hour for 6 hours.\textsuperscript{12-14}

However, the guide uses urine output and sCr values as staging criteria. In addition, because CSR is influenced by many factors and has low sensitivity and specificity for its
relationship with AKI, it is very important to determine other early AKI biomarkers that are more sensitive, specific, and significant. Markers that can be used for early diagnosis of AKI are Cystatin C, IL-18 (Interleukin-18), KIM-1 (Kidney Injury Molecule-1), L-FABP (Liver Fatty Acid Binding Protein), and NGAL (Neutrophil Gelatinase Associated Lipocalin).\textsuperscript{15-17}

IL-18 known as an inflammatory mediator, is produced by renal tubular epithelium and interstitial macrophages. IL-18 plays an active role in various kidney diseases, such as reperfusion injury, transplant rejection, and urinary tract infections. Levels of IL-18 are very physiologically low and increase several-fold in patients who experience AKI. Increased urine IL-18 levels in AKI are partly derived from damaged tubules.\textsuperscript{18-21}

In this study, based on the characteristics of the research subjects it can be seen that the sample of this study is heterogeneous. Research subjects who entered the ICU and HCU, as well as P1 were caused by a variety of medical, surgical, midwifery and neurology cases. The average age of 66 samples was 50 years. This result is the same as the Parikh study which also found an average age of AKI of 50 years with a male population of 52.2%, whereas in Chen's study, it was found that the average age of AKI was 60 years with 66% of men. This may be due to the diverse backgrounds of patients ranging from trauma cases that often occur at a young age to CVD which are more common in old age.\textsuperscript{22-27}

From 66 samples, 30 subjects (45.5%) diagnosed with Non-AKI, 22 subjects with stage 1 diagnosis of AKI (33.3%), 6 subjects with a diagnosis of AKI stage 2 (9.1 %) and 8 subjects with a diagnosis of AKI stage 3 (12.1%). From this data, the incidence of AKI in stage 1, stage 2 and stage 3 was 54.5%. This incidence is slightly different from the literature on the incidence of AKI in the HCU at 60-70%. The difference in incidence in this study may be due to differences in the number of samples.

A pilot study was conducted to obtain an IL-18 cut-off value of\textsuperscript{> 411.25 pg / mL} which showed positive AKI. The cut-off in this study differs from the research conducted by Haase in 2008 which received a cut-off value of\textsuperscript{> 750 pg / mL}, Endre in 2011 with a cut-off of 154 pg / mL and Doi in 2011 with a cut-off value 200.1 pg / mL. This cut-off difference is due to the number of samples used as pilot studies.

Based on bivariate analysis of the diagnostic values of AKI and IL-18, from 66 study samples 17 samples (77.27%) were found that had positive values both from the results of IL-18
and serum creatinine and 26 samples (59.1%) which had negative values from both checks. A total of 5 subjects (22.7%) showed false positives, and 18 subjects (40.9%) who showed false negatives. In this study also found that IL-18 had a sensitivity number of 48.6% and specificity of 83.9%, with an Odds ratio of 4.9111 (95% CI 1.5330 - 15.7328). This number of odds ratios shows that when IL-18 was obtained > 495 Pg / mL the possibility of diagnosing AKI was 4.9111 times greater.

The results of this study are similar to study, which proved that IL-18 can predict AKI with diagnostic odds ratios (OR) 5.1 with sensitivity and specific 0.51 and 0.79 respectively. Xin Lin also found that urine IL-18 levels in pediatric patients (18 years) were more effective in predicting AKI, with a diagnostic OR of 7.510 compared to 4.652 for the adult group (p = 0.334); subgroups of early predictive AKI time (12 hours) showed the highest diagnostic OR of 8,176 (95% CI 2,191-30,507) among three subgroups.28-31

**Conclusion**

The incidence of AKI in patients treated in the ICU, HCU and P1 in general hospital of Dr. Mohammad Hoesin Palembang at 54.5%. Urine IL-18 at levels > 411.25 Pg / mL has a sensitivity of 48.6%, specificity 83.9%, positive predictive value 77.27%, and negative predictive value 59.09%.

**References**


