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Assessment of the Renal Angina Index for Determining Acute Kidney Injury

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Abstract

Background: Oliguria or a rise in serum creatinine concentration has been performed to detect acute kidney injury (AKI); however, none of these methods is sensitive. Some pediatric researches used the renal angina index (RAI), which is beneficial to predict AKI.

Aim and objectives: Evaluation of the RAI efficacy in identifying critically sick individuals who were more likely to get severe AKI.

Patients and methods: In all, 50 patients who were hospitalized in ICUs participated in this prospective observational research. The patients were subjected to clinical examination and laboratory tests for blood urea, serum creatinine, complete blood picture, aspartate aminotransferase, alanine aminotransferase, albumin, electrolytes, and levels of serum calcium, phosphorus, sodium, and potassium. All patients were tested for urinary L-type fatty acid-binding protein (L-FABP) upon ICU admission. RAI was determined.

Results: The average age of the studied patients was 48.6 ± 13 years; 31 (62%) patients were males. The average BMI was 29.4 ± 4.6 kg/m². AKI was presented in 31 (62%) patients, of the patients 14 (45.2%) were of grade I AKI and 17 (54.8%) patients were of grade III AKI. There is increased urinary L-FABP in patients with AKI (14 ± 1.8) when compared with individuals without AKI (8.6 ± 1.0) and increased RAI in patients with AKI (21.4 ± 13) when compared with individuals without AKI (6.2 ± 7.4).

Conclusion: Diabetes mellitus, hypertension, elevated white blood cells, and chronic kidney disease were the most frequent risk factors for AKI. Patients with AKI had higher levels of urine L-FABP compared with those without AKI, and those with AKI had statistically significantly higher RAI than those without AKI.

Keywords: Acute kidney injury, ICU, Renal angina index

1. Introduction

Acute kidney injury (AKI) is acknowledged as a very common issue in critically sick patients and is closely linked to higher short-term and long-term death rates as well as higher resource use. AKI is a sudden decline in renal function that might take hours or days to manifest. This acute drop often shows up as a buildup of nitrogenous end products in the blood, such as urea and creatinine, and it sometimes goes hand in hand with oliguria.

AKI affects ~13 million people annually and kills 1.7 million people worldwide. In the poor world, AKI affects four out of every five patients. Up to 20% of inpatients and 30–60% of patients who are severely sick had AKI diagnosed. In ICUs, AKI is the greatest frequent etiology of organ dysfunction, and even moderate AKI is linked to a 50% increased chance of dying.

Several risk factors for the occurrence of AKI in the critical care setting have been identified. These factors are more nuanced rather than being single risk. Elderly patients seem to experience AKI more often than younger patients due to physiological aging of the kidneys, presence of comorbidities, and impaired renal capacity for recovery. Patients with
a history of diabetes mellitus (DM), hypertension (HTN), or underlying chronic kidney disease (CKD) have high susceptibility for renal injury that could result from the presence of renal damage from the underlying comorbidity, use of nephrotoxic drugs, or defects in the regenerating capacity of kidneys.6

The detection of severe AKI by serum creatinine is not ideal, and additional AKI indicators are developing. So, in order to start AKI prevention efforts, AKI prediction or risk classification of people at risk for kidney injury is essential.7 It has been shown that AKI indicators such as neutrophil gelatinase-associated lipocalin, tissue inhibitors of metalloproteinase-2 and insulin-like growth factor-binding protein 7, and L-type fatty acid-binding protein (L-FABP) might predict AKI.8 However, as they may be impacted by diseases and their function may decline in various situations, it is essential that these biomarkers be used in the proper setting. Thus, every patient admitted in the ICU must undergo a proper risk assessment for AKI.9 A recent proposal to risk stratify critically unwell children at increased risk of AKI used the renal angina index (RAI), which is established on alterations in renal performance.10

The purpose of the research was to evaluate the effectiveness of the RAI for identifying critically ill patients, who were more likely to experience severe AKI, identify the patterns and underlying causes of AKI in these patients, and evaluate the prognosis and outcomes of AKI in these patients.

2. Patients and methods

This prospective, observational research was conducted at the Intensive Care and Nephrology Units at Nasr City Hospital for Health Insurance on 50 severely sick patients hospitalized in the ICU of Nasr City Hospital for Health Insurance from June 2021 to the end of December 2021.

Their age ranged between 24 and 81 years with a mean age of 48.6 ± 13 years, of them 31 (62%) were males and 19 (38%) were females.

2.1. Inclusion criteria

Age more than 18 years or older and all critically ill patients with no AKI or AKI stage 1 at the time of admission.

2.2. Exclusion criteria

Patients under the age of 18 years, patients in AKI stages 2 or 3 at the time of ICU admission, patients with end-stage renal disease receiving regular hemodialysis, patients who have had kidney transplantation, and patients whose stay in the ICU was shorter than 48 h.

2.3. Methodology

The following procedures were applied to all patients.

2.4. History and clinical examination

Complete history taking from the patient or the relatives on admission, which include drug history (as utilization of NSAIDS, ACEIs, ARBs, and diuretics), the length of kidney disease, surgical operations, history of other comorbid conditions such as DM, cardiac disease, and liver cell failure. Full clinical examination: full clinical examination included assessment of the general condition with stress on the level of consciousness and vital signs (heartbeat, blood pressure, breaths per minute, and temperature). Examination of the abdomen, chest, and heart focused on looking for signs of chronic renal illness. Parameters for anthropometry were acquired. By dividing weight in kilos by height in square meters, the BMI is calculated. We estimated our height and weight. Having a blood pressure measurement of 140/90 mmHg or above is considered to have HTN. Diagnoses for diabetes were made using the following parameters: fasting blood glucose more than or equal to 126 mg/dl, glycosylated hemoglobin more than 6.5%, hypoglycemic drug use, or self-reported history of diabetes. Contrast exposure was defined as the delivery of intravenous contrast within 1 week of the start of AKI.

2.5. Laboratory investigations

Patients’ blood was drawn, and samples were sent to the following laboratories: complete blood picture tested by a cell counter (Sysmex XN-1000, Sysmex Corporation,1-5-1 Wakinohama-Kaigandori Chuo-Ku, Kobe 651-00073, Japan). Blood urea, serum creatinine, serum sodium, serum potassium, and serum calcium are among the renal function tests, and electrolyte levels were tested by an automated chemical analyzer (Cobas C311, Roche Diagnostics GmbH D-68298 Mannheim Germany).

2.6. Urinary L-type fatty acid-binding protein measurement

At the time of ICU admission, a new urine sample was taken from each patient. Enzyme-linked immunosorbent assay kit-based in vitro diagnostic
medical tests were used to detect the urine L-FABP level (Human L-FABP Assay Kit; CMIC Co. Ltd, Tokyo, Japan).

2.7. Assessment of acute kidney injury

The AKI network classification for AKI is a modified version of the older RIFLE classification, which required an elevated serum creatinine of at least more than or equal to 0.3 mg/dl (26.5 μmol/l) within a period of 48 h or by a reduction in urine output. AKI network considers AKI after getting sufficient hydration and after ruling out urinary tract occlusion.

AKI network staging for AKI.

2.8. Renal angina index

Each patient’s condition was graded according to the following scale: those receiving ventilation and/or vasopressor medication received five points; those with more than one comorbidity (such as DM, old age more than or equal to 70 years, CKD, or high blood pressure) received three points; and those who were enrolled to the ICU received one point. As a result, the RAI calculation did not take into account the information on the history of heart disorders, particularly chronic heart failure. The difference in serum creatinine between the time of ICU admittance and the latest 3 days prior was used to calculate the creatinine score, which was calculated as follows: eight points for creatinine more than 0.4 mg/dl, four points for creatinine more than 0.3 mg/dl, two points for creatinine more than 0.1 mg/dl, and one point for creatinine less than 0.1 mg/dl. The RAI score ranged between 1, 2, 3, 4, 6, 8, 10, 12, 24, and 40 and was calculated by multiplying the worst condition score by the creatinine score. In the first study, the following day after ICU admission, and in the second analysis, ICU admission, all patients were assessed for the RAI.

Consent form: every participant in the present research gave written permission after being informed of the purpose and specifics of the investigation. The Local Ethics Committee, Faculty of Medicine, Al-Azhar University, accepted the project.

2.9. Statistical analysis

Version 24 of the Statistical Program for the Social Sciences (SPSS, IBM Corp. Released 2016, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used to analyze the data. Quantitative information was presented as mean ± SD. Frequency and proportion were used to convey qualitative data. The mean (average) is the middle value in a collection of discrete numbers; it is the sum of values divided by the total number of values. The measure of a collection of values’ dispersion is the SD. When the SD is low, the values tend to be close to the set’s mean; when it is large, the values are dispersed across a broader range.

3. Results

There were 31 (62%) men and 19 (38%) females among the patients investigated. Regarding age, the average age of all patients evaluated was 48.6 ± 13.0 years, ranging from 24 to 81 years. The median BMI of all patients analyzed was 29.4 ± 4.6 kg/m², with a minimum BMI of 23.2 kg/m² and a maximum BMI of 44 kg/m². Regarding smoking, there were 31 (62%) smokers among the patients investigated (Table 1).

There were three (6%) patients with HTN, 15 (30%) patients with DM, five (10%) patients with CKD, and three (6%) patients with stroke, while there were no patients (0%) with cardiac diseases in the studied patients (Table 2).

Table 1. Description of demographic information for all patients investigated.

<table>
<thead>
<tr>
<th>Studied patients (N = 50)</th>
<th>Sex [% (%)]</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Smoking [% (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [% (%)]</td>
<td>Male</td>
<td>Female</td>
<td>Mean ± SD</td>
<td>Minimum–maximum</td>
</tr>
<tr>
<td></td>
<td>31 (62)</td>
<td>19 (38)</td>
<td>48.6 ± 13</td>
<td>24–81</td>
</tr>
</tbody>
</table>
Table 2. Description of underlying diseases in all patients investigated.

<table>
<thead>
<tr>
<th>Underlying diseases</th>
<th>Studied patients (N = 50) [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>3 (6)</td>
</tr>
<tr>
<td>DM</td>
<td>15 (30)</td>
</tr>
<tr>
<td>CKD</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Cardiac diseases</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Table 3 shows the description of AKI in all studied patients. AKI was present in 31 (62%) patients, of them 14 (45.2%) patients were of grade I AKI and 17 (54.8%) patients were of grade III AKI. As regards treatment, 20 (64.5%) patients received conservative treatment and 11 (35.5) patients received RRT.

Patients with AKI had a statistically substantial (P < 0.001) elevation in urine L-FABP (14 ± 1.8) as compared with those without AKI (8.6 ± 1.0). Patients with AKI had a statistically substantial (P < 0.001) rise in RAI (21.4 ± 13) compared with those without AKI (6.2 ± 7.4) (Table 4).

Urinary L-FABP can be used to distinguish between patients with AKI and those without AKI at a cutoff level of more than 10.75, with 94.1% sensitivity, 96.9% specificity, 96.8% positive predictive value (PPV), and 94.3% negative predictive value (NPV) (area under the curve = 0.99 and P < 0.001) (Table 5).

RAI can be used to distinguish between patients with AKI and those without AKI at a cutoff level of more than 16, with 46.9% sensitivity, 93.9% specificity, 88.5% PPV, and 63.9% NPV (area under the curve = 0.85 and P < 0.001) (Fig. 1).

4. Discussion

It is acknowledged that AKI is a highly common issue in severely sick patients and that it is closely linked to greater resource usage, as well as greater short-term and long-term mortality. AKI is a sudden decline in renal function that might take hours or days to manifest. This acute drop often shows up as a buildup of nitrogenous end products in the blood, such as urea and creatinine, and it sometimes goes hand in hand with oliguria.2

This research was conducted on 50 critically ill patients who were enrolled in ICUs of Nasr City Hospital for Health Insurance, from June 2021 to the end of December 2021.

As regards description of demographic data, the median age of all studied patients was 48.6 ± 13 years and 31 (62%) patients were males. The median BMI was 29.4 ± 4.6 kg/m². As regards underlying diseases, there were three (6%) patients with HTN, 15 (30%) patients with DM, five (10%) patients with CKD, and three (6%) patients with stroke.

AKI was present in 31 (62%) patients, of them 14 (45.2%) patients were of grade I AKI, and 17 (54.8%) patients were of grade III AKI.

Results of the current study showed statistically significant (P < 0.001) increased urinary L-FABP in patients with AKI (14 ± 1.8) when compared with those without AKI (8.6 ± 1.0).

We discovered that in critically sick adult patients, urinary L-FABP values at the time of ICU admission might be used to predict the onset of AKI.

In accordance with the current study, the Tony and colleagues conducted cohort research included 100 critically ill patients with risk indicators for AKI, who were hospitalized to the medical critical care units (CCUs). Urinary L-FABP showed higher median values in patients with AKI than in patients without AKI at the time of CCU admission. They discovered that adult critically sick patients’ urinary L-FABP values at the time of CCU admittance predict the onset of AKI within the first 7 days of their CCU stay.13

This result agreed with that of Doi et al.14 When 339 critically sick adult patients were admitted to a medical-surgical ICU, five distinct urine indicators (L-FABP, neutrophil gelatinase-associated lipocalin, cystatin C, interleukin-18, and albumin) were examined. Of these patients, 131 had AKI. They

Table 3. Description of acute kidney injury in all patients investigated.

<table>
<thead>
<tr>
<th>AKI</th>
<th>Studied patients (N = 50) [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Yes</td>
<td>31 (62)</td>
</tr>
<tr>
<td>AKI grade</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>Grade II</td>
<td>17 (54.8)</td>
</tr>
<tr>
<td>AKI treatment</td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td>RRT</td>
<td>11 (35.5)</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury.

Table 4. Relation between studied markers and acute kidney injury in patients investigated.

<table>
<thead>
<tr>
<th>AKI</th>
<th>MW</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (N = 33)</td>
<td>8.6 ± 1.0</td>
<td>14.0 ± 1.8</td>
</tr>
<tr>
<td>Yes (N = 17)</td>
<td>6.2 ± 7.4</td>
<td>21.4 ± 13.0</td>
</tr>
</tbody>
</table>

Urinary L-FABP (ng/dl)
Renal angina index

AKI, acute kidney injury; L-FABP, L-type fatty acid-binding protein; MW, Mann–Whitney U test.

P value less than 0.001 highly significant (HS).
found that urinary L-FABP was the most effective urine biomarker for detecting AKI.

According to the study’s findings, individuals with AKI had a statistically substantial ($P < 0.001$) higher RAI (21.4 ± 13) than those without AKI (6.2 ± 7.4). We discovered that in critically sick adult patients, RAI at the time of ICU admittance might indicate when AKI would start to develop.

In accordance with the current study, in the Molano-Trivino et al. retrospective study, 372 patients – 40.3% women – from 1204 new ICU patients, with a median age of 60.9 years, were included (18–98). In 26.8% of patients, AKI KDIGO two to three manifested. Patients with AKI had significantly different median creatinine levels at admission (confidence interval 0.95–0.51 to –0.15 mg/dl, $P = 0.0004$). Patients who had AKI were more likely to need hemodynamic ($P = 0.003$), ventilatory ($P = 0.009$), septic ($P = 0.003$), and coronavirus disease 2019 ($P = 0.03$) assistance. Thirty-nine (60%) patients with severe AKI needed renal replacement therapy (incidence 10.5%).

The Youden method’s RAI cutoff value for the whole sample was 24, and it was considerably greater in patients who had AKI (16.54 vs 7.47, confidence interval 0.95–13.5 – 4.99, $P < 0.001$). The strongest predictive ability for severe AKI needed a cutoff point of 24, with sensitivity, specificity, PPV, and NPV of 34%, 94%, 5.5, and 0.7, respectively. Multiple cohorts of critically sick children were tested for RAI, and the findings were comparable with renal angina in adults. Results obtained in this study were in agreement with Youssef et al. in which 53 critically ill children (34 males and 19 females) admitted to the pediatric ICU were included. They studied RAI and cystine C level in relation to standard pRIFLE using creatinine and urine output and its association to RAI. They revealed that there were statistically substantial variations in serum creatinine and blood urea on D3 and D7. They showed that 45 out 53 critically ill patients developed AKI. They observed that RAI predicts AKI with an accuracy of 94.3%, sensitivity of 84.6%, specificity of 97.5%, PPV of 91.7%, and NPV of 95.1%.

Similarly, Fahmy et al. conducted a cross-sectional study in Egypt that involved 100 full-term infants. They were grouped by the Neonatal Therapeutic Intervention Scoring System (NTISS) into 40 healthy infants, 30 infants manifested by clinical signs of moderate disorders of early neonatal period, 19 infants manifested by severe disorders without AKI, and 11 infants manifested by severe disorders and AKI. RAI was significantly higher in severely sick infants with AKI group IIB ($P < 0.5$ and 0.00, respectively). Receiver operating characteristic curves were plotted for those parameters to assess the best cutoff for the diagnosis of AKI. They observed that RAI more than 9 demonstrated a sensitivity of 81.82% and specificity of 87.76%.

### Table 5. Diagnostic performance of urinary L-type fatty acid-binding protein in the prediction of acute kidney injury.

<table>
<thead>
<tr>
<th>Cut off</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary L-FABP</td>
<td>&gt;10.75</td>
<td>0.99</td>
<td>94.1%</td>
<td>96.9%</td>
<td>96.8%</td>
<td>94.3%</td>
</tr>
<tr>
<td>RAI</td>
<td>&gt;16</td>
<td>0.85</td>
<td>46.9%</td>
<td>93.9%</td>
<td>88.5%</td>
<td>63.9%</td>
</tr>
</tbody>
</table>

AUC, area under the curve; L-FABP, L-type fatty acid-binding protein; NPV, negative predictive value; PPV, positive predictive value; RAI, renal angina index.

Fig. 1. ROC curve between patients with AKI and those without AKI as regards urinary L-FABP and RAI. AKI, acute kidney injury; L-FABP, L-type fatty acid-binding protein; RAI, renal angina index; ROC, receiver operating characteristic.
In 2014, Basu et al. performed a multicenter cohort research to examine the role of RAI in the early detection of AKI. Over the course of the included research sites, a total of 584 patients were evaluated, with sensitivity ranging from 58 to 93% and NPV ranging from 92 to 99%. For the prediction of severe AKI (>200% rise in serum creatinine), RAI was more sensitive and specific than neutrophil gelatinase-associated lipocalin, matrix metalloproteinase-8, and neutrophil elastase-2. In addition, RAI showed a considerably greater pretest probability as compared with KDIGO stages and pediatric risk of mortality.

The results of the current study observed that the common underlying diseases of AKI were DM (30%), CKD (10%), and HTN (6%). Among 15 patients with DM, nine had AKI. Among 11 patients with CKD, seven had AKI. There were three hypertensive patients, all of them had AKI. This result demonstrated that the risk factors of AKI were DM, HTN, and CKD.

The El-Badawy et al. study is a prospective, observational trial that included 50 critically sick ICU patients, who had just developed acute renal damage. Analysis of the research population's baseline data indicated that 68% of the participants were men, 62% of them had diabetes, 42% had HTN, 42% had a history of heart illness, 50% had persistent hepatic diseases, 48% had chronic kidney impairment, and 56% had cancers.

Our results showed that the mean white blood cell (WBCs) of all studied patients were 12.1 ± 7.3 with minimum WBCs of 3.2 and maximum WBCs of 31.2. There was statistically substantial \( P = 0.001 \) increased WBCs in patients with AKI (17.5 ± 9.1) when compared with patients without AKI (9.4 ± 4.2). There were 19 patients with increased WBCs, 15 of them had AKI (78.9%), and there were 31 patients with normal WBC count, and 17 (54.8%) of them had AKI. Using multivariate logistic regression analysis, the results of the current study observed that high WBCs could be used as a predictive factor of sepsis and subsequently AKI \( B = 0.17, SE = 0.057, P = 0.002, \text{odds ratio} = 1.19 \) and 95% confidence interval \( 1.06 - 1.33 \).

This result was supported by a study by Ab hamid et al. on 106 AKI patients who were admitted to the ICU. They said that sepsis was often the cause of AKI in patients (74.3%).

5. Conclusion

According to the results of our research, DM, HTN, raised WBCs, and CKD were all common risk factors for AKI. We also found that patients with AKI had higher urine L-FABP levels than those without AKI, and their RAI was statistically significantly \( P < 0.001 \) higher.

Funding

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Conflict of interest

There are no conflicts of interest.

References

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