Kidney injury molecule-1/creatinine as a urinary biomarker of acute kidney injury in critically ill neonates

Akram E. ElSadeka,*, Elham Abd El gafar a, Eman G. Behiry b, Siham A. Nazem c, Omima M. Abdel haie a

Introduction
Acute kidney injury (AKI) is a complex disorder, means acute deterioration of renal function generally occurring over hours to days. Serum creatinine (Scr) is a suboptimal biomarker in neonates as the creatinine concentration reflects the maternal level for up to 72 h after birth, to improve the ability for early prediction of AKI and improve clinical outcomes, there has been a significant amount of research to identify novel biomarkers of damage to allow for the earlier identification of neonates with AKI.

Objective
This study aimed to study the effectiveness of urinary kidney injury molecule-1/creatinine (uKIM-1/cr) in the diagnosis of AKI in critically ill neonates.

Study design
The patients’ group included 50 critically ill full-term septic neonates (39 of them developed AKI according to guidelines of AKI diagnosis), and control group including 50 healthy neonates. Full history taking, clinical assessment and laboratory testing of the renal functions (urea & creatinine), eGFR, uKIM-1 by ELISA technique and uKIM-1/cr ratio on admission, and on day 3 of admission.

Results
Urea, serum creatinine increased, whereas, eGFR decreased significantly in the second sample when compared to the first sample of the AKI group. uKIM-1 and uKIM-1/cr were high in the first sample, uKIM-1 concentration and uKIM-1/creatinine were higher in second sample (2.2/C6 0.6 ng/ml & 7.1/C6 2.1 ng/mg) when compared to first sample (0.6/C6 0.1 ng/ml & 2.6/C6 0.9 ng/mg) in critically ill neonates with AKI. Serum creatinine, uKIM-1 and uKIM-1/cr ratio were significantly associated with higher KDIGO stages. Applying the ROC curve at the first sample for discrimination between critically ill neonatal patients with and without AKI, uKIM-1/cr AUC was significantly higher when compared to AUCs of creatinine, eGFR, uKIM-1. Regression analysis revealed that high uKIM-1 & uKIM-1/cr are independent predictors for AKI within critically ill neonates. So, uKIM-1 & uKIM-1/cr are early biomarkers as their level increased before creatinine increases.

Conclusions
uKIM-1 and uKIM-1/cr are good early indicators for AKI in neonates suffering from a critical illness.
Introduction

Critical illness is a condition of advanced disease associated with rapidly deteriorating physiological functions up to organ failure and/or death within minutes or hours, requiring urgent appropriate care e.g. sepsis, respiratory impairment like airway obstruction or circulatory impairment or shock [1].

AKI is an acute impairment of kidney function disturbing the balance of fluid, electrolytes and waste products [2]. Any of the following is diagnostic of AKI in neonates: an acute rise of the serum creatinine (SCr) of at least 0.3 mg/dL within 48 h, a persistent rise of the SCr to 1.7 mg/dL for 3 days following birth, or a urine output less than 1 ml/kg/hr [3] yet, oliguria is not a sensitive marker of renal failure as it is not present in 50% of neonates [4].

Serum creatinine (SCr) reflects kidney function, not injury, thus at least 50% of the glomerular filtration rate should be lost before SCr increases [2]. Based on the current definition of AKI in adults and paediatrics, a significant number of neonates suffering from AKI are missed in studies that base their diagnosis of the elevated SCr [4].

Many biomarkers that could detect AKI early in neonates, allowing prevention as well as early management, have been identified including urinary neutrophil gelatinase-associated lipocalin, cystatin-c, and kidney injury molecule-1 [2].

KIM-1 is a type I transmembrane protein that participates in adhesion, growth, differentiation, regeneration and removal of dead epithelium by phagocytosis and is highly upregulated in the epithelium of the proximal tubule of the kidney. Normal kidneys produce KIM-1 in low amounts to be increased after insult induced by nephrotoxic compounds, then cellular regeneration occurs shedding KIM-1 antigen into the urine. The abnormally high excretion of KIM-1 in urine precedes casts excretion. There was less KIM-1 in the urine in less severe cases of AKI related to contrast exposure [5].

Urinary KIM-1 is more important than serum KIM-1, such dominance could be attributed to, firstly, its molecular size (90-kDa) preventing it from being reabsorbed by injured renal tubules, secondly its location in the cells of the apical surface of renal tubular cells, not the basolateral surface [6].

uKIM-1 has been reported as a highly efficient marker that differentiates true acute tubular necrosis from other renal insults [7]. This study evaluated the effectiveness of urinary kidney injury molecule-1 (uKIM-1) and urinary kidney injury molecule-1/creatinine (uKIM-1/Cr) in the prediction of acute kidney injury in critically ill neonates.

Subjects and methods

Setting and time of the study

This study was conducted during the period from July 2018 to June 2019 on critically ill neonates admitted to the Neonatal Intensive Care Unit (NICU) of Benha University Hospitals.

Details of the subjects recruitment (patients/controls)

50 full term critically ill neonates (critical illness is defined as: a life-threatening process that is in the absence of medical intervention is expected to result in mortality or significant morbidity [1]), diagnosed by clinical manifestations and laboratory markers of neonatal sepsis [8] who were at risk to develop acute kidney injury (AKI).

Critically ill neonates fulfilling the diagnostic criteria of the KDIGO for neonatal AKI, acute rise of the serum creatinine (SCr) of at least 0.3 mg/dL within 48 h or a persistent rise of the SCr to 1.7 mg/dL for 3 days following birth was diagnostic for AKI [3]. Accordingly, participants were assigned to either an AKI group, 39 neonates (24 males and 15 females), or a non-AKI group, they were in AKI group 11 neonates (6 males and 5 females). The control group included healthy 50 neonates matched with the first group in gestational age and birth weight.

Preterm neonates, congenital anomaly of kidney or chromosomal abnormalities were excluded from this study.

Caregivers of the participants signed informed written consents before joining the study which followed the World Medical Association Declaration of Helsinki and approval of the ethical committee of Banha University was granted for its protocol [9].

Study design

A prospective case-controlled study.

Study protocol

- Complete history taking and Full clinical examination
- Laboratory Investigation:

  Blood sample: was taken at day 1 (first sample) and day 3 (second sample) of admission for assessment of serum urea and creatinine.

  Urine samples: were obtained in conjunction with serum sampling of creatinine at day 1 and day 3 of admission for evaluation of uKIM-1 and urine creatinine level in both samples.
Techniques used to collect, measure, and analyze data

Blood sample: Three ml of blood was taken in an empty test tube (without anticoagulant) and kept at room temperature for 30 min to coagulate then centrifuged at 1500 rpm for 15 min and the separated serum was collected for assessment of serum urea and creatinine. Urine samples were collected through placing urine bags and the urine was centrifuged for 10 min and preserved at -40 C until used for assessment of uKIM-1 and creatinine.

Laboratory investigations

The resultant serum was used for renal function tests. Serum and urine creatinine were measured using the BioSystems reagent kit of the BioSystems S.A. (Barcelona, Spain) by a modified Jaffe reaction. Serum urea was measured via applying the enzymatic colourimetric test, using a Diamond kit, (Diamond Diagnostics, Holliston, USA), done by Biosystem autoanalyizer BT3500 (Barcelona Spain). Estimated creatinine clearance is measured by Schwartz formula: eGFR = 0.413 × (height/Scr) if the height is expressed in centimeters or 41.3 × (height/Scr) if the height is expressed in meter [10].

Urinary KIM-1: was conducted using a kit that was purchased from SunRed Biotechnology Company (Shanghai, China), with Cat No: 201-12-1100. The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). The ratio between uKIM-1 and creatinine was calculated.

Statistical analysis

The data collected were given a code and analyzed by SPSS version 16 (SpssInc, Chicago, ILL Company). Descriptive statistics for categorical variables included frequency, absolute and relative percentage, and for normally distributed numerical variables included mean and standard deviation. Statistical tests of significance used included Kruskal–Wallis test for non-parametric analysis, Shapiro–Wilks test for normality of quantitative data, assuming normality at P > 0.05, Chi-square (χ²) test or Fisher’s exact test (FET) for categorical data, Student “t” test for normally distributed variables among two independent groups, Mann Whitney U test for non-parametric variables, Spearman’s correlation coefficient (rho) for linear associations between variables and Multiple regression analysis to detect significant predictors. The cutoff value, as well as the optimum specificity and sensitivity, were identified by the ROC curve. P-values below 0.05 were perceived as significant [11].
Table 3  Comparison of renal function tests (urea, creatinine, eGFR), uKIM-1 and uKIM-1/creatinine between first and second samples in studied critically ill neonates with and without AKI.

<table>
<thead>
<tr>
<th></th>
<th>First sample</th>
<th>Second sample</th>
<th>Neatons without AKI N = 11</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>Mean ± SD</td>
<td>33.7 ± 7.3</td>
<td>46.5 ± 21.1</td>
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<tr>
<td></td>
<td>Min-max</td>
<td>24–45</td>
<td>28–101</td>
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</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>Mean ± SD</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>0.4–0.9</td>
<td>0.4–1.1</td>
<td></td>
</tr>
<tr>
<td>Urine creatinine (mg/dl)</td>
<td>Mean ± SD</td>
<td>31.8 ± 4.8</td>
<td>32.3 ± 4.6</td>
<td>0.231</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>26–44</td>
<td>24.7–41.8</td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>Mean ± SD</td>
<td>33.8 ± 10.3</td>
<td>32.2 ± 9.2</td>
<td>0.231</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>22.91–52.69</td>
<td>18.7–49</td>
<td></td>
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<tr>
<td>uKIM-1 (ng/ml)</td>
<td>Mean ± SD</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.501</td>
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<tr>
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<td>Min-max</td>
<td>0.3–0.7</td>
<td>0.4–0.8</td>
<td></td>
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<tr>
<td>uKIM-1/Creatinine (ng/mg)</td>
<td>Mean ± SD</td>
<td>1.5 ± 0.4</td>
<td>1.9 ± 0.5</td>
<td>0.131</td>
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<tr>
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<td>Min-max</td>
<td>0.8–2.3</td>
<td>0.3–2.4</td>
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<table>
<thead>
<tr>
<th></th>
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<th>Second sample</th>
<th>Neatons with AKI N = 39</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>Mean ± SD</td>
<td>32.5 ± 10.1</td>
<td>41.9 ± 17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>14–83</td>
<td>20–101</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>Mean ± SD</td>
<td>0.5 ± 0.1</td>
<td>1.2 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>0.3–0.9</td>
<td>0.6–2.5</td>
<td></td>
</tr>
<tr>
<td>Urine creatinine (mg/dl)</td>
<td>Mean ± SD</td>
<td>33.2 ± 4.6</td>
<td>35.6 ± 4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>23.3–44</td>
<td>22.1–41.8</td>
<td></td>
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<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>Mean ± SD</td>
<td>40.2 ± 12.9</td>
<td>19.6 ± 7.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>22.91–70.25</td>
<td>7.6–32.8</td>
<td></td>
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<tr>
<td>uKIM-1 (ng/ml)</td>
<td>Mean ± SD</td>
<td>0.6 ± 0.01</td>
<td>2.2 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>0.2–0.8</td>
<td>0.9–4.6</td>
<td></td>
</tr>
<tr>
<td>uKIM-1/Creatinine (ng/mg)</td>
<td>Mean ± SD</td>
<td>2.6 ± 0.9</td>
<td>7.1 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>1.2–4.5</td>
<td>2.7–12.5</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; min, minimum; max, maximum. Numerical data were tested using paired sample t-test.

**Results**

The present study was conducted on 50 critically ill full-term neonates (39 of them develop AKI and 11 did not develop AKI). They were 30 males (60%) (24 of them develop AKI and 6 did not develop AKI) and 20 females (40%) (15 of them develop 5 did not develop AKI). Mean gestational age of cases was 38.2 ± 1.1 (37–39) weeks, mean weight was 3.1 ± 0.4 (2.5–4.4) kgs and postnatal age was 2 h–23 days. While control group gestational age was 37.9 ± 0.5 (37.1–40) weeks, mean weight was 3.2 ± 0.4 (2.6–4.3) kgs and postnatal age was (3 h–22 days).

Higher frequency of maternal diabetes (DM), hypertension (HTN), premature rupture of membrane (PROM), accidental haemorrhage and drug intake in critically ill neonates with AKI than those without AKI (Table 1).

No significant differences were found in renal functions (urea, serum creatinine, and eGFR) at first sample between cases and control groups as well as between critically ill patients with and without AKI. While uKIM-1 concentration at first sample and uKIM-1/creatinine were significantly higher in critically ill neonates with AKI than those without AKI as well as the control group (Table 2).

Urea, serum creatinine increased, whereas, eGFR decreased significantly in the second sample when compared to the first sample of the AKI group (Table: 3). No significant differences were found in serum urea, serum creatinine, eGFR and uKIM-1 between first and second samples in studied critically ill neonates without AKI.

uKIM-1 concentration and uKIM-1/creatinine were significantly higher in second sample (2.2 ± 0.6 ng/ml & 7.1 ± 2.1 ng/mg) when compared to first sample (0.6 ± 0.1 ng/ml & 2.6 ± 0.9 ng/mg) in critically ill neonates with AKI (Table: 3).

All studied cases diagnosed with AKI were stratified by KDIGO classification; 21 cases had class I (53.8%), 12 cases had class II (30.8%) and 6 cases had class III (15.4%).

Serum creatinine, uKIM-1, and uKIM-1/creatinine ratio were significantly associated with higher KDIGO stages.

Otherwise, no significant associations were found in other renal functions (urea, urine creatinine and eGFR) according to KDIGO classification in all studied cases (Table 4).

uKIM-1 and uKIM-1/creatinine in second sample positively correlated with serum creatinine (r = 0.797 & p = 0.001& r = 0.754& p = 0.001 respectively), and a negative correlation with eGFR (r = −0.720 & p = 0.001& r = −0.685& p = 0.001 respectively). Otherwise, no significant correlations were found between uKIM-1 or uKIM-1/creatinine level at first or second samples with other studied renal functions in all critically ill neonatal patients (Fig. 1a and b & Fig. 2a and b).
Applying Receiver operating characteristic curve (ROC) on the first day for discrimination between critically ill neonatal patients with and without AKI, uKIM-1/creatinine AUC was significantly higher (0.858) than AUCs of serum creatinine, eGFR, uKIM-1 (0.506, 0.648, 0.716 respectively). uKIM-1 AUC (0.716) was significantly higher when compared to the AUC of serum creatinine and eGFR (0.506, 0.648) (Fig. 3).

Urinary KIM-1 at a cut off value of 0.55 ng/ml was 56.4% sensitive and 90.9% specific marker of AKI in neonates suffering from a critical illness with PPV, NPP (95.7, 37) respectively. While uKIM-1/creatinine at a cut off value of

<table>
<thead>
<tr>
<th>Kdigo classification</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 21</td>
<td>N = 12</td>
<td>N = 6</td>
<td></td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>Mean ± SD</td>
<td>30.3 ± 6.1</td>
<td>31.6 ± 10.2</td>
<td>36.6 ± 16.4</td>
</tr>
<tr>
<td>Min-max</td>
<td>14</td>
<td>50</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>Mean ± SD</td>
<td>0.6 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>1 ± 0.3</td>
</tr>
<tr>
<td>Min-max</td>
<td>0.3</td>
<td>0.9</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Urine creatinine (mg/dl)</td>
<td>Mean ± SD</td>
<td>31.9 ± 4.5</td>
<td>33.1 ± 5</td>
<td>34.2 ± 3.4</td>
</tr>
<tr>
<td>Min-max</td>
<td>23.3</td>
<td>41</td>
<td>23.3</td>
<td>41</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>Mean ± SD</td>
<td>42.9 ± 13.5</td>
<td>38.2 ± 12.7</td>
<td>34.9 ± 8.8</td>
</tr>
<tr>
<td>Min-max</td>
<td>22.9</td>
<td>70.2</td>
<td>24.3</td>
<td>68.1</td>
</tr>
<tr>
<td>uKim-1 (ng/ml)</td>
<td>Mean ± SD</td>
<td>0.41 ± 0.11</td>
<td>0.52 ± 0.12</td>
<td>0.66 ± 0.14</td>
</tr>
<tr>
<td>Min-max</td>
<td>0.23</td>
<td>0.72</td>
<td>0.34</td>
<td>0.74</td>
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<tr>
<td>uKim-1/Creatinine (ng/mg)</td>
<td>Mean ± SD</td>
<td>2.1 ± 0.9</td>
<td>2.9 ± 0.9</td>
<td>3.5 ± 1.0</td>
</tr>
<tr>
<td>Min-max</td>
<td>1.2</td>
<td>3.8</td>
<td>1.2</td>
<td>4.1</td>
</tr>
</tbody>
</table>

<, one way ANOVA.

Fig. 1 Correlation of uKIM-1 level with A- Creatinine and b-eGFR in the second sample in critically ill neonates with AKI.
1.9 ng/mg was 76.9% sensitive and 90.9% specific marker with PPV, NPP of (96.8, 52.6) respectively.

Logistic regression analysis was conducted for early detection of AKI in neonates suffering from a critical illness, using gender, gestational age (GA), urea, creatinine, urine creatinine, eGFR, uKIM-1, uKIM-1/creatinine at the first day as covariates. High uKIM-1 level, uKIM-1/creatinine were considered as independent early predictors for AKI within critically ill neonates. So, uKIM-1 and uKIM-1/creatinine were early biomarkers as their level increased before creatinine increased with the superiority of uKIM-1/creatinine (Table 5).

Discussion

KIM-1 is a transmembrane type-1 epithelial cell protein have a role in tubulointerstitial damage. Tubular KIM-1 expression was detected after toxic or ischemic injury in humans. Also, uKIM-1 was linked with ischemic acute tubular necrosis and have better predictive value for detecting AKI (Genc et al. 2013).

In our study, renal functions (urea, creatinine, and eGFR) revealed no significant change between patients (with and without AKI) and control in the first sample while a significant increase in urea, creatinine level and significant decrease in eGFR level was observed in AKI patients in the second sample when compared to the first sample. This agrees with El-Farghali et al., [12] who reported significantly higher blood urea and serum creatinine were in neonates suffering from a critical illness and AKI than those without AKI and the control group as well at the second sample.

In a study done by Abdelaal et al., [13] they found that in the first sample (day 1–3 of life) the mean of serum creatinine values was insignificantly different in neonates with AKI, neonates with no AKI and controls, while the second sample (7 days of life) demonstrated a significantly higher serum creatinine in neonates with AKI than those with no AKI and controls which was in agreement with our results.

Our results revealed a significant increase in uKIM-1 and uKIM-1/creatinine in the first sample and were significantly higher in the second sample when compared to the first sample.
sample in critically ill patients with AKI and their rise occurred before the rise in serum urea & creatinine and decrease in eGFR.

In agreement with our results, Genc et al.,[14] who found in their study that uKIM-1 was elevated early in the first sample and significantly increased in the second sample (3 days after admission) than the first sample (at admission) as a result of the advancement of AKI in critically ill neonates.

Also in agreement with our study Van Timmeren et al.,[15], reported an early elevation of the uKIM-1 in renal patients versus controls (p < 0.001).

El-Gamasy and Nassar.,[16] assessed factors which predispose to AKI in 190 neonates suffering from hypoxic-ischemic encephalopathy (HIE), they were divided into two groups; neonates meeting neonatal AKI diagnostic criteria served as cases (group1) and neonates without AKI served as controls (group2). This study reported that the neonates in the two studied groups had no significant difference in initial blood urea or serum creatinine values at the time of admission. This observation clarified that initial normal blood urea and/or serum creatinine levels cannot exclude AKI and emphasized the significance of serial follow up measurements of blood urea and/or serum creatinine levels.

Chiusolo et al. [17] revealed that up-regulation of KIM-1 gene expression can be detected with mild renal morphological changes or before these changes. Hoffmann et al. [18] reported that uKIM-1 is a sensitive marker for early nephrotoxic changes, before functional abnormalities are observed and both agree with our results.

Table 5  Regression analysis for early detection (first sample) of AKI within critically ill neonates.

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.677</td>
<td>0.846</td>
<td>0.385 1.857</td>
<td>0.385</td>
<td>1.857</td>
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<tr>
<td>Gestational age</td>
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<td>0.961</td>
<td>0.758 1.218</td>
<td>0.758</td>
<td>1.218</td>
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<tr>
<td>Urea</td>
<td>0.754</td>
<td>0.995</td>
<td>0.962 1.029</td>
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<tr>
<td>Serum Creatinine</td>
<td>0.994</td>
<td>0.991</td>
<td>0.106 9.239</td>
<td>0.106</td>
<td>9.239</td>
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<tr>
<td>Urine creatinine</td>
<td>0.380</td>
<td>1.039</td>
<td>0.953 1.133</td>
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<tr>
<td>eGFR</td>
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<td>1.029</td>
<td>0.991 1.067</td>
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<td>uKIM-1</td>
<td>&lt;0.001</td>
<td>2.873</td>
<td>1.301 8.318</td>
<td>0.032</td>
<td>1.390</td>
<td>1.002 3.463</td>
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<td>uKIM-1/Creatinine</td>
<td>&lt;0.001</td>
<td>3.265</td>
<td>1.287 6.265</td>
<td>0.001</td>
<td>2.580</td>
<td>1.101 7.098</td>
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</table>

OR, odds ratio; CI, confidence interval; logistic regression analysis was used.

Fig. 3  ROC of serum creatinine, eGFR, urinary KIM-1, uKIM-1/creatinine at first day for discrimination between critically ill neonates with and without AKI.

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In our results, a significant increase in serum Cr in the AKI group with advanced KDIGO stages was found, also uKIM-1 and uKIM-1/creatinine showed a significant increase with advanced KDIGO classes.

Similar to this study, Liu et al., [19] reported an association between the level of uKIM-1 and the severity of kidney injury concluding it to be a sensitive, noninvasive, and quantitative diagnostic as well as monitoring marker for kidney damage.

In our results, the uKIM-1 second sample showed a positive correlation with serum creatinine, a negative correlation with eGFR. Similarly, Genc et al., [14] reported a positive correlation between the rise of uKIM-1 and that of the creatinine.

Van Timmeren et al., [15] reported a positive correlation between the urinary KIM-1 and the tissue KIM-1 and a negative correlation between negatively the urinary KIM-1 and eGFR, concluding it as a non-invasive early marker of kidney damage which was in agreement with our study.

Also, Liu et al., [20] reported uKIM-1 as a reliable marker for renal damage and attributed that being confined to the injured epithelium of the proximal tubules sparing the healthy tubular tissue and being continually shed in urine starting 12 h of the insult till regeneration of the epithelium.

In our study, the ROC curve at first sample revealed that creatinine AUC failed eGFR showed poor AUC, uKIM-1 AUC was good, while uKIM-1/creatinine AUC was very good. uKIM-1/creatinine AUC was significantly higher when compared to AUCs of creatinine, eGFR and uKIM-1. So, uKIM-1/creatinine was the best, followed by uKIM-1, followed by creatinine and eGFR for discrimination of critically ill neonates with and without AKI.

Similarly, Shao et al., [21] reported uKIM-1, which is 74.0% sensitive and 86.0% specific with a DOR of 17.43 (95% CI, 6.23–48.74), as an efficient diagnostic marker of AKI.

We also agreed with Tekce et al., [22] who reported that regarding the diagnosis of AKI, the urinary KIM-1 was 87.5% sensitive, 93.3% specific with 93.3% negative predictive values and AUC of 0.83.

Regarding AKI, Youssef et al., [23] reported that the sensitivity of the serum creatinine and eGFR was poor while the specificity of which was high in contrast to uKIM-1 for which the sensitivity was 86% and the specificity was 100% with a cut off value of 1.5. Similar to this study, Paramastuty et al., [24] found that AUC of uKIM-1 at admission 0.850 (>0.7) with a p-value of 0.040, so it can be used to predict AKI in critically ill neonates.

In our results, high uKIM-1 level, uKIM-1/creatinine were considered as independent predictors for AKI in critically ill neonates. We agreed with research conducted by Liangos et al., [25] who studied 6 urinary biomarkers in cardiac surgery patients, uKIM-1 has a good performance to predict AKI 2 h after surgery with AUC 0.78 and reported that the cutoff value of uKIM-1 to detect AKI was 0.42 ng per milligram of creatinine (sensitivity: 92%, specificity: 58%).

We are in accordance with Lim et al., [26] concluded in their study that uKIM-1 levels were significantly elevated within a few hours after kidney damage before serum creatinine rise. A study was done by Genc et al., [14] detected that an increase of 0.5 ng per milligram of uKIM-1/creatinine from day 1 to day 3 was the cut off value to predict AKI (AUC:0.791).

Duan et al., [27] found that the predictable time of acute kidney injury (AKI) onset determined by uKIM-1, was 24 h earlier than by serum creatinine. So uKIM-1 could be an early predictive biomarker as compared with serum creatinine. Which agreed with our study.

Zhang and his colleges [28] documented that NGAL was a promising biomarker of septic AKI. Like the uKIM-1, the sKIM-1 could early predict the occurrence of septic AKI too, but both of them did not have the predictive value in assessment the prognosis of sepsis or severity of AKI.

The study has some limitations, as the small sample size. Larger studies on uKIM-1 and other different urinary markers could recognize AKI sooner than Scr. Future studies in larger cohorts are required to determine which biomarkers at which time points can best predict different etiologies of neonatal AKI.

Conclusion

uKIM-1 & uKIM-1/creatinine are good indicators for early diagnosis of AKI in critically ill neonates. The uKIM-1/creatinine ratio is more sensitive than uKIM-1 alone or serum creatinine in early detection of AKI in critically ill neonates.

Fund

No fund.

Ethical approval

This study protocol was approved by ethical review board of Benha University. Written, informed consent was obtained from each patients included in the study.

Conflicts of interest

No conflict of interest.

References

Kidney injury in critically ill neonates


