Urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin are early predictors for acute kidney injury among patients admitted to the surgical ICU

Mohammed F Abosamak[a] and Adel F Alkholy[b]

[a]Department of Anesthesia & ICU, Faculty of Medicine, Tanta University, Tanta, Egypt; [b]Department of Medical Biochemistry, Faculty of Medicine, Benha University, Benha, Egypt

ABSTRACT

Objectives: Evaluation of urinary neutrophil gelatinase-associated lipocalin (UNGAL) and kidney injury molecule 1 (UKIM-1) as early predictors of development of acute kidney injury (AKI) in patients admitted to surgical ICU.

Patients & Methods: 188 ICU patients were clinically evaluated and gave blood samples for estimation of at admission (T0) serum creatinine (SCr) and urine samples for estimation of urinary creatinine (UCr), UNGAL and UKIM-1 and their values were adjusted to UCr level. At 48-hr after admission SCr levels were re-estimated and AKI was diagnosed and staged according to the Acute Kidney Injury Network criteria. Study outcomes included the ability of estimated markers for prediction of possible AKI development.

Results: At 48-hr after ICU admission, 73 patients (38.8%) developed AKI; 42, 21 and 10 mild, moderate and severe AKI, respectively. At T0, UNGAL and UKIM1, and their UCr ratios showed progressive increase with increased AKI grade. Calculated ΔSCr was positively correlated with clinical data and estimated levels of urinary markers. Regression analysis defined elevated BMI, TISS-28 score, UNGAL and UKIM-1 as early significant predictors for AKI. ROC curve analysis defined UNGAL and UKIM-1 and their ratios to UCr as the significant predictors for AKI development.

Conclusion: Development of AKI in ICU patients was related to severity of surgical trauma. High UNGAL and UKIM-1 at time of ICU admission can predict upcoming AKI and its AUC after adjustment to UCr levels had superior predictive value for AKI. A high uKIM-1/UCr ratio can be considered the most significant early predictor for AKI.

1. Introduction

Acute kidney injury (AKI) is the most common cause of organ failure in multiple organ dysfunction syndrome [1] and despite advances in medical technologies and interventions, the incidence of AKI continues to rise [2]. AKI is a life-threatening illness, which is associated with a high in-hospital mortality rate ranging between 20% and 50% according to the underlying conditions [3].

Acute kidney injury is a frequent event among critically ill patients and is associated with increased morbidity and mortality [4] especially for septic patients [5], after major abdominal surgery [6], open thoracic aortic surgery [7], cardiac surgeries especially in patients with congenital heart disease [8].

Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the lipocalin protein family which is characterized by similar structure, but has diverse functions [9]. Human NGAL is a 25-kDa secretory glycoprotein consists of 178-amino acid and exists in three molecular forms, including a 25-kDa monomer, a 45-kDa homodimer, and a 135-kDa disulfide-linked heterodimer bound to latent matrix metalloproteinase-9 [10]. NGAL has dual effects as a siderophore: iron-binding protein and as a growth factor, and is markedly induced in kidney tubule cells, massively upregulated after renal tubular injury, so it may participate in limiting kidney damage [11]. NGAL was detected in plasma and urine in animal models of ischemic, septic and nephrotoxic AKI [12] and can differentially suggest the site of kidney injury where detection of the monomeric and dimeric forms of uNGAL suggest upper and lower urinary tract origins of disease, respectively [13].

Kidney injury molecule-1(KIM-1) is a type I membrane protein consisting of extracellular and cytoplasmic portions [14]. KIM1 is an epithelial phosphatidylserine receptor expressed transiently after acute kidney injury and chronically in fibrotic renal disease, promotes kidney fibrosis [15]. KIM1 is the most highly upregulated protein in the renal proximal tubule after injury and its ectodomain which is heavily glycosylated and stable is released into the lumen of the tubule and appears in the urine after injury [16]. KIM-1 acts as a double-edged sword that is implicated

in both injury and healing of the kidney [17] as it is markedly upregulated in injured and regenerating renal proximal tubular epithelial cells following ischemic or toxic insults [18].

2. Hypothesis

Early prediction of AKI can help to improve patients' outcome through early institution of the appropriate intervention [5], thus the current study hypothesized that urine analysis for certain markers may provide an early knowledge about the possibility of oncoming kidney affection secondary to organ and tissue trauma affecting patients admitted to surgical ICU.

3. Objectives

The current study tried to evaluate the value of urinary markers as early predictors of possible development of AKI in patients admitted to surgical ICU.

4. Setting

Anesthesia & ICU Department, Security Forces Hospital, Riyadh, KSA

5. Design

Prospective observational three-year study

6. Patients & methods

All patients who were admitted to surgical ICU since Nov 2016 were eligible for evaluation for inclusion and exclusion criteria. Patients with manifest kidney disease, who had renal surgery, maintained on renal replacement therapy or had diabetic nephropathy were excluded from the study. Also, patients who had liver disease, endocrinopathies, morbid obesity that was defined as body mass index (BMI) >35 kg/m^2 [19] were also excluded from the study.

All patients were clinically evaluated for demographic and clinical data. Severity of injury and number of surgical interventions were evaluated using the simplified Therapeutic Intervention Scoring System (TISS-28) which evaluates the extent of injury of the body as divided into six major areas and each surgical intervention is assigned 1 to 4 points and the points are summed to obtain an overall score [20]. The extent of impact of associated diseases on patients' physiological and body organs' functions was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE II) [21] and sequential organ failure assessment (SOFA) [22]. Higher scores indicate more severe illness and for the TISS-28 score, each therapeutic intervention is assigned 1 to 4 points, and the points are summed daily to obtain the overall score and higher score indicates a higher number of therapeutic interventions.

7. Diagnosis of AKI

Development of AKI within the first 48 hours after ICU admission and its staging was defined according to the Acute Kidney Injury Network criteria. Each stage was defined by the extent of change in serum creatinine level (ΔSCr) as follows: Mild if Scr was increased by ≥0.3 mg/dL or ΔSCr was ≥1.5-2-fold from baseline, Moderate if ΔSCr was >2-3-fold from baseline and Severe if ΔSCr was increased by >threefold from baseline [23].

8. Laboratory investigations

(A) Blood samples were drawn under complete aseptic conditions at time of ICU admission (T0) and 48 hours thereafter (T48). Blood samples were put in clean dry tube and allowed to clot to separate serum for estimation of serum creatinine (SCr) using an enzyme linked immunosorbent assay (ELISA) kit (catalog no. ab65340; Abcam, Cambridge, USA) [24].

(B) Urine sample
- Sampling: Catheter tubing with sampling port was inserted in the catheter orifice, urine was assured to flow in the tube, a clamp was applied about 6 cm below the level of the sampling port to allow urine to collect above the clamp so that a sample can be obtained. Sampling port was swabbed with alcohol-impregnated swab and allowed to dry, tubing was holding below the level of the sampling port, a syringe tip was inserted into the sampling port and 10-ml of urine was aspirated and then the clamp was released to allow urine to drain freely.
- Processing & preservation: Urine was put into a sterile tube, centrifuged at 2000 *g* for 20 minutes, and the supernatant was frozen at − 80°C till being assayed within 4 months using ELISA kits according to the manufacturer's instructions and were read using a 96 well microplate ELISA reader (Dynatech MR 7000)
- Investigations

1. Spot Urinary creatinine (UCr) was estimated using the same procedure applied for SCr estimation [24].
2. Urinary human neutrophil gelatinase-associated lipocalin (U-NGAL) was estimated using an ELISA kit (catalog no. ab215541; Abcam, Cambridge, USA) by sandwich enzyme-linked immunosorbent assay

technology according to manufacture instructions. The limit of NGAL detection with this research assay is 46.9–3000 pg/ml [25,26].

3. Urinary human kidney injury molecule 1 (U-KIM1) was estimated using an ELISA kit (catalog no. ab235081; Abcam, Cambridge, USA) by sandwich enzyme-linked immunosorbent assay technology according to manufacture instructions. The limit of KIM1 detection with this research assay is 7.81–500 pg/ml [27].

9. Study outcomes

(1) The primary outcome is the ability of estimated urinary markers and their ratio in relation to urinary creatinine to be used as early predictors for patients susceptible to develop AKI. Early predictor was defined as a marker that changed early well before serum creatinine rise so as to allow prevention or treatment at very early stage of AKI [28,29] (Han et al., 2008; Liangos et al., 2009). The formulas used to calculate urinary KIM-1 and NGAL to urinary creatinine ratios were uKIM-1/Cre = KIM-1/Creatinine (pg/g) and uNGAL/Cre = NGAL/Creatinine (ng/g) [30] (Żyłka et al., 2018).

(2) The secondary outcomes include:
   a. The number of patients who developed ΔSCr diagnostic of AKI and the extent of AKI severity.
   b. The results of statistical analyses for the best predictor for upcoming AKI.

10. Statistical analysis

Obtained data were presented as mean±SD, numbers and percentages. Results were analyzed using paired t-test, One-way ANOVA Test and Chi-square test (X^2 test). Possible relationships were investigated using Pearson's correlation analysis. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors. Sensitivity & specificity of studied parameters as predictors for patients' outcome were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) that was compared versus null hypothesis that AUC = 0.5. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P-value < 0.05 was considered statistically significant.

11. Results

Two hundred and seventeen patients were admitted to surgical ICU for varied indications, 29 patients were excluded from the study for not fulfilling inclusion criteria, while 188 patients were included in the study. At time of admission, estimated SCr showed non-significant difference between patients who developed AKI (AKI group) and those who were free of AKI at 48-hr after admission (No AKI group). At 48-hr after ICU admission, all patients had elevated SCr with significantly higher T48-SCr levels in comparison to T0-SCr levels and 73 patients (38.8%) developed T48-SCr levels diagnostic for AKI. Forty-two patients (22.3%) had mild, 21 patients (11.2%) had moderate and 10 patients (5.3%) had severe AKI, while 115 patients (61.2%) had T48-SCr levels that were not diagnostic for AKI (Table 1, Figure 1).

Demographic and clinical data of studied patients categorized according to development and severity of AKI showed non-significant differences apart from TISS-28 scores that were significantly lower in patients with no AKI in comparison to patients with AKI as shown in Table 2.

Mean levels of urinary creatinine (UCr) showed gradual decrease through AKI grades with significant difference versus no AKI. On contrary, urinary NGAL and KIM1 levels estimated at time of ICU admission showed progressive increase with increased AKI grade with significantly higher levels in AKI patients in comparison to no AKI. Adjustment of uNGAL and uKIM1 in relation to UCr levels assured the progressive increase with the increased AKI severity and showed significant differences in comparison to levels estimated in patients of No AKI group (Table 3).

There was positive significant correlation between ΔSCr and patients' age, BMI, APACHE II, SOFA and TISS-28 scores and with estimated levels of urinary markers as well as their adjusted ratio to UCr level while ΔSCr showed positive non-significant correlation with male gender. Moreover, estimated levels of urinary markers showed positive significant correlation with each other and with TISS-28 scores. Estimated UNGAL levels showed positive significant correlation with APACHE scores, while estimated UKIM-1 levels were positively correlated with SOFA scores (Table 4).

Regression analysis defined elevated BMI (β = 0.111, p = 0.001), TISS-28 score (β = 0.099,

Table 1. Patients' distribution according to the development and severity of AKI as judged by change in serum creatinine.

Time Group	T0-SCr (mg/dL)	T48-SCr (mg/dL)	ΔSCr
No AKI (n = 115)	0.888 ± 0.134	1.077 ± 0.165	1.19 [IQR: 1.12–1.28]
AKI Mild (n = 42)	0.903 ± 0.236	1.61 ± 0.42	1.8 [IQR: 1.7–1.8]
Moderate (n = 21)	0.978 ± 0.25	2.34 ± 0.25	2.3 [IQR: 2.2–2.6]
Severe (n = 10)	0.988 ± 0.324	3.446 ± 1.188	3.5 [IQR: 3.325–3.725]
Total (n = 73)	0.938 ± 0.205	2.072 ± 0.778	1.9 [IQR: 1.8–2.5]
Total patients (n = 188)	0.948 ± 0.13	1.54 ± 0.72	1.19 [IQR: 1.12–1.28]

Data are presented as mean, standard deviation, median [IQR]; SCr: Serum creatinine; T0: time at admission, T48: at 48 hr after admission; ΔSCr: the extent of change in SCr; AKI: acute kidney injury.
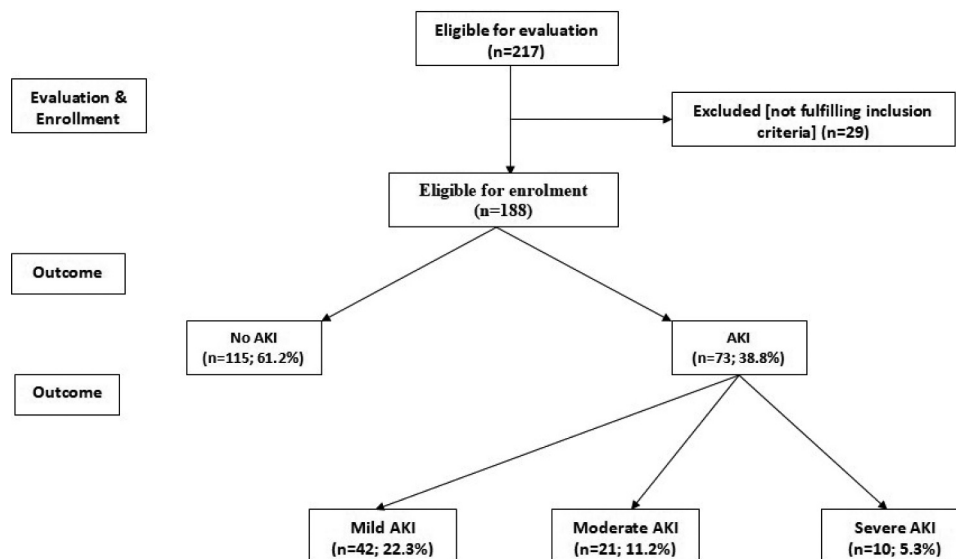
Figure 1. Consort flow sheet.

Table 2. At admission data of patients categorized according to development and severity of AKI.

Group Variable		No AKI (n = 115)	AKI (n = 73) Mild (n = 42)	Moderate (n = 21)	Severe (n = 10)	P1	P2	P3
Age (years)		43.8 ± 10.3	41.8 ± 11	46.4 ± 10.1	47 ± 10.7	0.295	0.286	0.345
Sex	Males	78 (67.8%)	24 (57.1%)	13 (61.9%)	6 (60%)	0.214	0.596	0.613
	Females	37 (32.2%)	18 (42.9%)	8 (38.1%)	4 (40%)			
Weight (kg)		84.6 ± 6.5	84.8 ± 6.9	84 ± 6.9	85.8 ± 6.6	0.885	0.681	0.586
Height (cm)		170.3 ± 3.2	169.9 ± 2.7	169.3 ± 2.6	171 ± 3.4	0.426	0.153	0.536
BMI (kg/m²)		29.16 ± 2	29.37 ± 2.25	29.35 ± 6.78	29.32 ± 1.84	0.562	0.702	0.807
APACHE II score		16 ± 3.8	17.7 ± 3.5	18.4 ± 3.9	18.8 ± 3.7	0.101	0.109	0.093
SOFA score		9 ± 2.1	9.5 ± 1.8	9.4 ± 2.9	10.4 ± 2.2	0.214	0.286	0.371
TISS-28		32.3 ± 11.8	38.9 ± 13.4	40 ± 15	48.4 ± 1.7	0.003	0.008	0.0001
Cause of ICU admission	Cardiac	32 (27.8%)	8 (19%)	6 (28.6%)	3 (30%)			
	Chest	8 (7%)	3 (7.1%)	1 (4.8%)	1 (10%)			
	Abdominal	29 (25.2%)	10 (23.9%)	4 (19%)	2 (20%)	0.589	0.885	0.959
	Trauma	19 (16.5%)	7 (16.7%)	3 (14.3%)	1 (10%)			
	Sepsis	27 (23.5%)	14 (33.3%)	7 (33.3%)	3 (10%)			

Data are presented as mean, standard deviation, numbers, percentages; AKI: Acute kidney injury; BMI: Body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; TISS-28: simplified Therapeutic Intervention Scoring System; P1 indicates the significance of difference between patients developed mild AKI and patients free of AKI; P2 indicates the significance of difference between patients developed moderate AKI and patients free of AKI; P3 indicates the significance of difference between patients developed severe AKI and patients free of AKI; P < 0.05 indicates significant difference; P > 0.05 indicates non-significant difference.

Table 3. At admission laboratory findings of studied patients categorized according to development and severity of AKI.

Group Variable	No AKI	AKI Mild	Moderate	Severe	Statistical significance P1	P2	P3
UCr (mg/dL)	1.29 ± 0.24	1.119 ± 0.33	1.084 ± 0.33	0.683 ± 0.28	0.00006	0.00008	<0.0001
UNGAL (ng/ml)	71.6 ± 35.7	231.1 ± 62.6	330.2 ± 107.8	429.5 ± 191.8	<0.0001	<0.0001	<0.0001
UNGAL/UCr	55.7 ± 29	221.7 ± 83.2	308.6 ± 89.6	712.5 ± 422.1	<0.0001	<0.0001	<0.0001
UKIM1 (pg/ml)	36.4 ± 18.2	119.7 ± 44.1	214.5 ± 51	232.5 ± 93.7	<0.0001	<0.0001	<0.0001
UKIM1/UCr	27.7 ± 10.3	113.5 ± 52.2	207.9 ± 66.7	370.4 ± 176.7	<0.0001	<0.0001	<0.0001

Data are presented as mean, standard deviation; AKI: Acute kidney injury; UCr: Urinary creatinine; U-NGAL: Urinary neutrophil gelatinase-associated lipocalin; U-KIM1: Urinary kidney injury molecule 1; P1 indicates the significance of difference between patients developed mild AKI and patients free of AKI; P2 indicates the significance of difference between patients developed moderate AKI and patients free of AKI; P3 indicates the significance of difference between patients developed severe AKI and patients free of AKI; P < 0.05 indicates significant difference; P > 0.05 indicates non-significant difference.

p = 0.003), urinary NGAL (β = 0.615, p < 0.001) and KIM-1 (β = 0.499, p < 0.001) levels estimated at time of admission as the early significant predictors for upcoming AKI. ROC curve analysis defined urinary levels of NGAL and KIM-1 and their ratios to UCr as the significant predictors for development of AKI (Table 5, Figure 2).

12. Discussion

The current study detected a 38.8% incidence of AKI among patients admitted to surgical ICU, irrespective of the indication of ICU admission. The reported rate coincided with that reported by early studies which evaluated the incidence of AKI in surgical ICU and

Table 4. Pearson's correlation between development and severity of AKI as judged by ΔSCr and patients' demographic, clinical and lab data.

		ΔSCr	UNGAL	UKIM1
Age	r	0.188	0.114	0.105
	P	0.010	0.672	0.781
Male gender	r	0.076	0.064	0.046
	P	0.303	0.385	0.527
BMI	r	0.157	0.104	0.095
	P	0.032	0.124	0.093
APACHE II	r	0.248	0.161	0.142
	P	0.001	0.028	0.053
SOFA	r	0.162	0.083	0.149
	P	0.026	0.259	0.042
TISS-28	r	0.331	0.316	0.269
	P	<0.001	<0.001	0.001
UNGAL	r	0.763	-	0.769
	P	<0.001	-	<0.001
UNGAL/UCr	r	0.372	-	-
	P	<0.001	-	-
UKIM1	r	0.810	0.769	-
	P	<0.001	<0.00	-
UKIM1/UCr	r	0.833	-	-
	P	<0.001	-	-

"r": Pearson's coefficient; ΔSCr: difference between serum creatinine at 48-hr and at admission levels; BMI: Body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; TISS-28: simplified Therapeutic Intervention Scoring System; UCr: Urinary creatinine; U-NGAL: Urinary neutrophil gelatinase-associated lipocalin; U-KIM1: Urinary kidney injury molecule 1; P indicates the significance of the correlation; P < 0.05 indicates significant difference; P > 0.05 indicates non-significant difference.

Table 5. Area under the ROC curves for urinary NGAL and KIM-1 and their ratio to UCr for early prediction of AKI development within 48-hr after ICU admission.

Variables	AUC	SE	95% CI	P value
UNGAL	0.589	0.042	0.508–0.678	0.039
UKIM-1	0.593	0.043	0.509–0.678	0.031
UNGAL/UCr	0.605	0.043	0.520–0.689	0.016
UKIM-1/UCr	0.686	0.038	0.610–0.761	<0.001

AUC: Area under curve; SE: Standard error; CI: Confidence interval; UCr: Urinary creatinine; U-NGAL: Urinary neutrophil gelatinase-associated lipocalin; U-KIM1: Urinary kidney injury molecule 1.

reported incidence rates of 44% among general population of patients admitted to surgical ICU [31], 14% in patients with sepsis, shock, major surgery, and trauma [32] and 13.4% among pediatrics admitted to trauma surgical ICU [33]. Moreover, the reported figure also coincided with recent studies that detected AKI incidence of 19.4% at 48-hr after abdominal surgery [6], 34.8% after isolated coronary revascularization [34], 44% in ICU septic patients [35] and 46.9% after robot-assisted laparoscopic radical prostatectomy [36]. However, these discrepant figures for incidence could be attributed to the differences in the studied population.

Serum creatinine levels estimated at 48-hr after ICU admission were significantly higher in all patients' samples in comparison to levels estimated at time of admission; a finding illustrative of the surgery &/or anesthesia-induced kidney insult, irrespective of the progress to AKI or not. In support of this finding, the incidence of AKI showed positive significant correlation with TISS-28 score which illustrates the multiplicity

and severity of surgical interferences and with APACHE II score which manifest the impact of disease and surgery on patients' physiology. In line with these findings, Zorrilla-Vaca et al. [37] detected that ASA III–IV and open surgical approach are independent risk factors for AKI, and Xu et al. [38] found radical not partial nephrectomy was an independent risk factor for AKI. Moreover, AKI incidence showed positive significant correlation with patients' age and BMI. Similarly, multiple recent studies detected that age, male gender, BMI and body surface area are independent risk factors for postoperative AKI [37,39–41].

The extent of increased 48-SCr level (ΔSCr) was significantly higher in AKI than in No AKI patients, but it has no predictive ability for upcoming AKI. Similarly, UCr level showed progressive decrease with AKI severity and can be used as severity measure but also has no predictive value. On contrary, urinary levels of NGAL and KIM1 estimated at time of ICU admission showed significant difference between AKI and No AKI patients with positive significant correlations with AKI severity as manifested by increased ΔSCr and with increased APACHE and TISS-28 scores. ROC curve analysis of patients' variables defined both UNGAL and UKM1 as early predictors to discriminate patients who are liable to develop AKI prior to the increase of serum creatinine, and on adjustment in relation to UCr levels, ROC curve defined UKIM1/UCr ratio as the significant predictor for upcoming AKI with more significant difference in AUC versus the null hypothesis than AUC for UNGAL/UCr.

In line with these findings, NGAL Meta-analysis Investigator Group [42] concluded that urinary and plasma NGAL concentrations can identify patients at high risk for AKI in clinical research and practice. Also, Törnblom et al. [35] using ROC curve analysis found the corresponding AUCs for uNGAL were 0.690, 0.728, 0.769, and 0.600 for discrimination of AKI, severe AKI, renal replacement therapy and mortality of patients admitted to ICU with sepsis. Moreover, Rashidi et al. [43] found NGAL was analytically superior to traditional AKI biomarkers such as creatinine and urine output for early prediction of AKI in sepsis and trauma patients and Fatani et al. [44] found urinary KIM-1 levels were significantly associated with sepsis severity and AKI. Furthermore, Darawshi et al. [45] found that increased urinary and serum NGAL in ICU patients who developed AKI while on inhibitors of sodium-glucose co-transporter-2 indicates acute tubular injury that principally affecting distal tubular segments. Similarly,

Unfortunately, few studies had evaluated the diagnostic ability of serum or urinary KIM1 in ICU setting, however, the obtained results go in hand with studies that evaluated KIM1 as biomarker for kidney affection in other settings as with Quang et al. [46] who found urinary KIM-1 and NGAL are independent markers for early diagnosis of diabetic nephropathy with higher
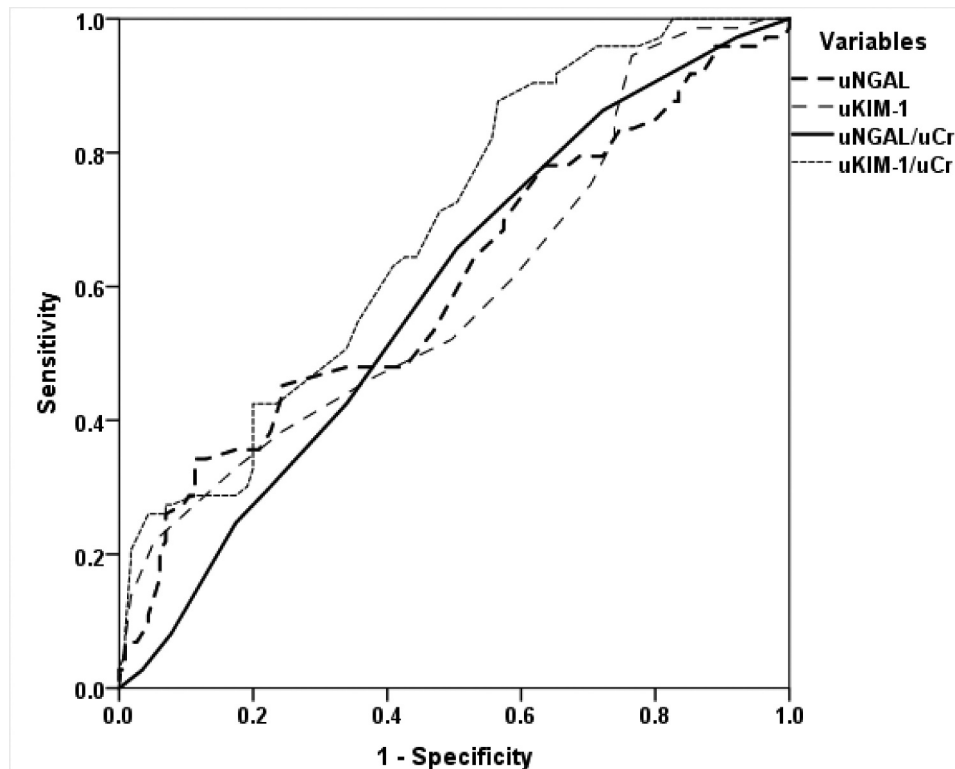
Figure 2. ROC curve analysis for urinary markers as early predictors for upcoming AKI.

AUC for KIM1 as sensitive early marker and Khalil et al. [47] who found high preoperative KIM1 level in morbidly obese patients undergoing sleeve gastrectomy correlate with serum creatinine and can discriminate patients with microalbuminuria and decreased postoperative KIM1 levels indicated kidney recovery.

13. Conclusion

Development of AKI in patients admitted to surgical ICU is a frequent complication with an incidence of 38.8% that was related to patients' demographic data and severity of surgical trauma. High urinary levels of NGAL and KIM-1 at time of ICU admission can predict upcoming AKI and its AUC after adjustment to urinary creatinine levels had superior predictive value for AKI than other variables. High UKIM-1/UCr ratio can be considered the most significant early predictor for AKI.

14. Limitation

The study was limited by being a single-center study and by the use of only two markers for evaluation.

Disclosure statement

No potential conflict of interest was reported by the authors.

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