Serum Neutrophil Gelatinase-Associated Lipocalin and Urinary Kidney Injury Molecule-1 as Potential Biomarkers of Subclinical Nephrotoxicity After Gadolinium-Based and Iodinated-Based Contrast Media Exposure in Pediatric Patients with Normal Kidney Function

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Background: New renal biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) show promise in early diagnosis of contrast media induced acute kidney injury (CI-AKI). The purpose of our study was to compare the subclinical nephrotoxicity (a condition without changes in standard renal biomarkers) of gadolinium-based contrast media (Gd-DTPA, gadopentetate dimeglumine) and iodinated-based contrast media (iopromide) in pediatric patients with normal kidney function.

Material/Methods: The first group (n=58) of patients included in the study were undergoing angiography with iopromide, and the second group (n=65) were undergoing magnetic resonance (MR) angiography/urography with Gd-DTPA administration. The concentrations of NGAL and KIM-1 were measured four times in the urine (pre-contrast, then at four hours, 24 hours, and 48 hours after contrast administration), and serum NGAL was measured at 0 (baseline), 24 hours, and 48 hours after contrast exposure.

Results: After 24 hours, serum NGAL increase of ≥25% was noticed in 32.6% of the patients in the iopromide group and in 25.45% of the patients in the gadolinium group, with significantly higher average percent of this increase in first group (62.23% vs. 36.44%, p=0.002). In the Gd-DTPA group, we observed a statistically significant increase in urinary KIM-1 24 hours after the procedure. Normalized urinary KIM-1, 24 hours after contrast exposure, was a better predictive factor for CI-AKI than other biomarkers (AUC 0.757, cut off 214 pg/mg, sensitivity 83.3%, specificity 54.2%, p=0.035).

Conclusions: In children with normal renal function, exposure to iodinated-based and gadolinium-based media might lead to subclinical nephrotoxicity, which could be detected using serum NGAL and urinary KIM-1.

MeSH Keywords: Acute Kidney Injury • Child • Contrast Media • Gadolinium

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/903255
Background

Radiocontrast media administration is one of the important causes of acute kidney injury (AKI), mostly reported in adult patients. Contrast induced-AKI (CI-AKI) occurs in up to 15% of the general population receiving intravascular iodinated-based contrast media (ICM) [1]. Limited comparable detailed data in children is available; the first major retrospective analysis of AKI in a pediatric tertiary care center identified nephrotoxins as an important cause, occurring in 17% of cases [2]. Gadolinium chelate based contrast media (GBCM) are considered to be safe and not nephrotoxic in standard magnetic resonance imaging (MRI) procedures. However, its use has been questioned on the basis of reports of nephrotoxicity [3,4]. Many clinical studies and some case reports of GBCM-associated AKI have been published [5–7]. However, the topic of GBCM-induced nephrotoxicity remains highly controversial. While the term “injury” does not necessarily imply dysfunction, the diagnosis of AKI is still made on the basis of a change in serum creatinine (SCr) or a drop in urine output, as manifestations of an acute decline in the glomerular filtration rate (GFR). However, it is well known that SCr is an unreliable indicator during acute changes in kidney function [8]. Recently, considerable attention has been paid to signs of structural damage to the nephrons, summarized in a meta-analysis of a novel renal marker, neutrophil gelatinase-associated lipocalin (NGAL) [9]. In children who have undergone a cardiopulmonary bypass (CPB), it has been reported that patients with prominent elevations of NGAL in serum and urine over two hours after the operation tend to develop AKI later [10]. Hirsch et al. reported that an elevation of NGAL in the serum and urine of children who underwent a cardiac catheterization using a contrast medium can be a predictive factor for CI-AKI [11]. It is obvious that kidney injury may occur even in the absence of a parallel or consequent alteration of kidney function. Thus, substantial proportions of patients are believed to acquire subclinical AKI. Hence, many definitions of AKI and CI-AKI have been revised, like those in the European Society of Urogenital Radiology (ESUR) Contrast Media Safety Committee guidelines, pRIFLE (pediatric Risk Injury Failure Loss End Stage kidney), and AKIN (Acute Kidney Injury Network), which incorporate, as minimal diagnostic criteria, a decrease in the estimated GFR of at least 25% or changes in SCr as low as 26.5 μmol/L (0.3 mg/dL) [12]. Several studies [1,13,14] have used acute cystatin C change to define AKI using a definition similar to the SCr-defined AKI. Validation studies have demonstrated that such marginal conditions are associated with worse outcomes [15]. Additional markers are on the horizon, including the kidney injury molecule-1, a renal regenerative protein [12,16]. The future direction is the incorporation of some of these new biomarkers in CI-AKI diagnostic criteria.

There is little or no data on the use of gadolinium-based and iodinated-based contrast media in patients, particularly children with normal renal function, and their evaluation using novel biomarkers of subclinical acute kidney injury. Thus, we conducted a prospective case-control study to compare nephrotoxicity of Gd-DTPA and iopromide when used for MRI and cardiovascular angiography in patients with normal kidney function. In addition to conventional tests, early novel AKI biomarkers (serum and urinary NGAL, urinary KIM-1) were also used to assess subclinical changes in the kidneys of our patients.

Material and Methods

Patients and study design

We performed a prospective study of 123 children and adolescents (51 females and 72 males) undergoing contrast media (CM) exposure in a single center from January 1, 2013 to December 31, 2015. The first group (n=58) of patients with acyanotic congenital heart disease underwent angiography with a low osmolar non-ionic, iodine-based contrast administration (iopromide, Ultravist® 370). The second group (n=65) consisted of patients with suspected urinary tract anomalies who underwent MR angiography/urography with gadolinium-based contrast administration (gadopentetate dimeglumine, Magnevist®). Exclusion criteria included: age under two years, chronic kidney disease (those with estimated creatinine clearance below age adjusted normal), cyanosis, diabetes mellitus, and concomitant nephrotoxic drug use. None of the patients in the iopromide group were in congestive heart failure. Also, patients in the Gd-DTPA group had normal urinary tract findings or mild physiologic variation (mild pyelocaliceal dilatation, duplication, simple cysts) without organic obstruction which did not have an impact on renal function. We therefore studied two homogenous populations of pediatric patients with no major confounding variables in whom the only obvious renal insult would be the result of CM administration. All patients in group I (iopromide group) received iopromide injection in doses adjusted for body weight and determined by the number and location of cardiovascular angiograms. The patients in this group were hydrated intravenously with 3 mL/kg/hour of fluid during the procedure. The subjects in group II (Gd-DTPA group) received gadopentetate dimeglumine intravenously in doses adjusted for body weight (0.1–0.2 mL/kg) and concomitant nephrotoxic drug use. None of the patients in this group were and urine over two hours after the operation tend to develop AKI later [10]. Hirsch et al. reported that an elevation of NGAL in the serum and urine of children who underwent a cardiac catheterization using a contrast medium can be a predictive factor for CI-AKI [11]. It is obvious that kidney injury may occur even in the absence of a parallel or consequent alteration of kidney function. Thus, substantial proportions of patients are believed to acquire subclinical AKI. Hence, many definitions of AKI and CI-AKI have been revised, like those in the European Society of Urogenital Radiology (ESUR) Contrast Media Safety Committee guidelines, pRIFLE (pediatric Risk Injury Failure Loss End Stage kidney), and AKIN (Acute Kidney Injury Network), which incorporate, as minimal diagnostic criteria, a decrease in the estimated GFR of at least 25% or changes in SCr as low as 26.5 μmol/L (0.3 mg/dL) [12]. Several studies [1,13,14] have used acute cystatin C change to define AKI using a definition similar to the SCr-defined AKI. Validation studies have demonstrated that such marginal conditions are associated with worse outcomes [15]. Additional markers are on the horizon, including the kidney injury molecule-1, a renal regenerative protein [12,16]. The future direction is the incorporation of some of these new biomarkers in CI-AKI diagnostic criteria.
biochemical serum and urine analyses were performed. All serum and urine samples (for NGAL and KIM-1) were received at room temperature and centrifuged (3000 rpm for 10 minutes) within one hour of arriving at the laboratory; sample supernatants were then frozen at -80°C, until assayed. Serum and urine creatinine levels were measured by the hospital clinical laboratory using a modification of the kinetic Jaffé reaction on a Dimension autoanalyzer (Siemens Healthcare GmbH, Germany). Estimated GFR (eGFR) was assessed according to the formula of Schwartz et al. [17]. The study was approved by the Research Ethics Board of the Medical School of Belgrade and complied with the Declaration of Helsinki. Written informed consent from the legal guardian, and written assent from children when available, were obtained before enrollment.

Biomarker measurements

Serum cystatin C, sNGAL, uNGAL, and uKIM-1 were assayed using human-specific commercially available enzyme-linked immunoassays (ELISA) (R&D Systems, Inc., Minneapolis, MN, USA), according to the manufacturer’s recommendations.

Statistical analysis

Descriptive statistics are shown as mean ± standard deviation for continuous variables. Nonparametric data were expressed as median (interquartile range-IQR). Results of two groups were compared by t-test for quantitative data and Fisher’s exact test for proportions. Repeated measures ANOVA were used for the comparison of changes in serum creatinine, eGFR, cystatin C, sNGAL, uNGAL, uKIM-1 and various solute excretions in both groups. Pearson’s correlation coefficients were used to compare serum creatinine, eGFR, cystatin C with novel biomarkers. Logistic regression analyses were done for biomarkers prediction of CI-AKI occurrence. Receiver-operating characteristic (ROC) curves and the area under the curve (AUC) were constructed to describe the performance of biomarkers and their normalized values at 24 hour post-CM exposure. The sensitivity and specificity of these biomarkers for predicting CI-AKI was then calculated. The best cutoff value for this biomarker was chosen on the basis of maximum sensitivity and specificity. Calculation of the study power and sample size was performed according to the criteria for the AKI diagnosis of about 25% of creatinine rise. Although this was a small sample study, its strength was the fact that it was a prospective study with homogenous patient population and the calculated sample size required to demonstrate significance power of 80% was achieved. Statistical Package for social science (SPSS) program version 23 was performed and statistical significance was set at \( p<0.05 \).

Results

Baseline characteristics and demographic data

A total of 123 children and adolescents were recruited and divided in two groups according to the type of CM administration. The mean eGFR for all patients was 133.40±25.89 ml/min/1.73 m² and the mean SCr was 63.52±18.30 µmol/L at baseline. There were 72 boys and 51 girls with a mean age of 12.54±4.62 years. Table 1 shows baseline clinical characteristics of patients included in the study. The changes in SCr, cystatin C, eGFR, serum NGAL, urinary NGAL, and urinary KIM-1 after cardiac angiography and MRI are shown in Tables 2 and 3. In Gd-DTPA group at 24 hours post exposure, the serum NGAL was highly associated with SCr and cystatin C, respectively, (\( r=0.498, p<0.001 \); \( r=0.353, p=0.008 \), respectively).

Subclinical CI-AKI

In the iopromide group, after 24 hours, the serum NGAL rose higher than in the Gd-DTPA group but without statistical significance between the two groups (\( \Delta SNGAL 4.3 \text{ ng/mL (IQR 16.55)}, \Delta \text{NGAL 0.7 ng/mL (IQR 16.6)}, p=0.992 \)). At the same time point, serum NGAL increased ≥25% from baseline in 32.6% of patients who received iopromide and in 25.5% of patients who received Gd-DTPA. The median increase in this subgroup of patients was 62.23% in the iopromide group and 36.44% in the Gd-DTPA group \( (p=0.002) \). In the Gd-DTPA group, after 24 hours, the urinary KIM-1 rose higher than in the iopromide group \( (\Delta uKIM-1 32.05 \text{ pg/mL (IQR 204.3)}, P=0.019; \Delta uKIM-1 24.0 \text{ pg/mL (IQR 151.3)}, p=1.0) \). But, the difference between the two groups was not statistically significant \( (p=0.318, \text{Figure 1}) \).

Frequency and early diagnosis of CI-AKI

The incidence of CI-AKI, as defined according to the new criteria as a decrease in GFR of ≥25% or increase in SCr of ≥25% (or at least 26.5 µmol/L) of their baseline values within 48 hours of contrast exposure, was higher in the Gd-DTPA group, but without statistical significance. In the iopromide group, two patients (3.9%) were diagnosed with CI-AKI, as were six patients (9.7%) in the Gd-DTPA group. Since an unsteady creatinine volume output due to varying degrees of dilution may influence the data considerably, we used both non-normalized and normalized urinary biomarkers (KIM-1 and NGAL).

The results of the ROC analyses for the normalized urinary KIM-1 showed the AUC of the uKIM-1/UCr at 24 hours post CM exposure was 0.757 (95% confidence interval (CI): 0.629–0.885, \( p=0.035 \)). At 24 hours after CM exposure, values in normalized urinary KIM-1 with concentrations >214 pg/mg had a sensitivity of 83.3%, and a specificity of 54.2% for the early detection of CI-AKI (Table 4). On the other hand, the AUC of the serum
NGAL, urinary NGAL, uNGAL/uCr, and uKIM-1 were lower and without statistical significance for CI-AKI prediction (Table 4).

**Discussion**

Iodinated radiocontrast media-induced acute kidney injury (CI-AKI) is well described and common in at-risk populations. Because GBCM have characteristics very similar to those of ICM, in particular hyperosmolality and renal clearance entirely dependent on glomerular filtration, nephrotoxicity was an obvious concern. However, GBCM have significantly lower viscosity and are used at significantly lower volumes (4 to 11 times less than ICM), making them potentially less nephrotoxic [18]. In animal models, Elmståhl et al. demonstrated that the histomorphological changes caused by gadolinium are similar to those caused by ICM and are not related to the dose of CM in ischemic porcine kidneys [19]. In humans, early studies revealed that GBCM are relatively safe molecules in healthy participants [20] and in patients with chronic kidney disease [21]. Since renal tubules are nearly always damaged during CI-AKI, changes in SCr and GFR do not indicate tubular damage.

### Table 1. Baseline clinical characteristics and laboratory parameters in groups.

| Characteristics | Iopromide (n=58) | Gd-DTPA (n=65) | p   |
|-----------------|------------------|----------------|-----|
| Age* (years)    | 11.9±4.9         | 13.1±4.2       | ns  |
| Sex (Female/Male) | 22/36            | 29/36          | ns  |
| BMI (kg/m²)     | 19.7±4.2         | 20.6±3.6       | ns  |
| ACEI/ARBs (no[%]) | 7 (12.1%)       | 11 (16.9%)     | ns  |
| Serum creatinine* (µmol/l) | 60.1±18.3 | 66.5±14.0 | ns  |
| eGFR* (ml/min/1.73m²) | 135.0±23.4 | 121.9±26.4 | ns  |
| Cystatin * (mg/ml) | 0.75±0.19     | 0.76±0.2       | ns  |
| [Ua/Ucr]spot urine ** (mg/mmol) | 1.2 (1.24) | 1.48 (1.82) | ns  |
| [Upr/Ucr]spot urine ** (mg/mg) | 0.14 (0.09) | 0.12 (0.12) | ns  |
| sNGAL* (ng/ml) | 44.3±18.6        | 49.2±15.8      | ns  |
| uNGAL** (ng/ml) | 32.2 (180.9)    | 10.35 (88.5)  | ns  |
| uKIM-1** (pg/ml) | 327.5 (195)   | 236.2 (273)*  | ns  |
| Volume of contrast agent* (ml) | 104.4±60.9 | 10.7±4.3     | <0.01 |
| Dose of contrast agent* (ml/kg) | 2.7±2.0     | 0.20±0.03     | <0.01 |

BMI – body mass index; ACEI – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; eGFR – estimated glomerular filtration rate; Ua/Ucr – albumin/creatinin ratio in spot urine; Upr/Ucr – protein/creatinin ratio in spot urine; sNGAL and uNGAL – serum and urinary neutrophil gelatinase-associated lipocalin; uKIM-1 – urinary kidney injury molecule-1; * Mean ± standard deviation (SD); ** Median ± IQR (interquartile range).

### Table 2. Changes in serum creatinine, cystatin C, serum and urinary NGAL and urinary KIM-1 after iodine contrast exposure.

| Variables            | Baseline | 4 h after procedure | 24 h after procedure | 48 h after procedure | p   |
|----------------------|----------|---------------------|---------------------|---------------------|-----|
| Creatinine(µmol/l)   | 60.1±18.3| nm                  | 66.5±15.9*          | 62.5±17.4*          | <0.01|
| Cystatin (mg/l)      | 0.75±0.19| nm                  | 0.76±0.15*          | 0.76±0.14           | ns  |
| sNGAL (ng/ml)        | 44.3±18.6| nm                  | 51.7±18.7           | 47.1±15.4           | ns  |
| uNGAL (ng/ml)        | 32.2 (180.9)| 7.85 (84.8)   | 28.8 (289.4)        | 29.7 (201.9)        | ns  |
| uKIM-1 (pg/ml)       | 327.8 (195) | 255.5 (205.7) | 320.4 (256.2)       | 312.2 (180.6)       | ns  |
| uKIM-1/uCr (pg/mg)   | 278.7 (289.0) | 202.2 (299.6)       | 258.8 (329.3)       |       |

sNGAL and uNGAL – serum and urinary neutrophil gelatinase-associated lipocalin; uKIM-1 – urinary kidney injury molecule-1; uKIM-1/uCr – KIM-1/creatinine ratio in spot urine; nm – not measured; * p<0.05 vs. 0 h.

NGAL, urinary NGAL, uNGAL/uCr, and uKIM-1 were lower and without statistical significance for CI-AKI prediction (Table 4).
damage. In recent decades, a number of novel and predictive biomarkers, such as KIM-1, NGAL, and cystatin C, have been developed which provide earlier and more specific detection of CI-AKI [12]. In our study, according to the most recent criteria for the occurrence of CI-AKI (a rise in SCr of 25% at 48 hours after CM application), two children (3.9%) in the group that was given the iodine contrast and six children (9.7%) in the group that was given the gadolinium contrast developed AKI. The finding for the latter group of children is unexpectedly high. However, this is similar to the report by Duan at al. in which they studied elderly patients with normal kidney function. In their study, eight out of 60 (13.3%) patients undergoing enhanced MRI using GBCM developed CI-AKI [22]. Since only two patients who received iopromide in our study met the criteria for CI-AKI, our results suggest that a low osmolar, non-ionic ICM for intravascular use, such as iopromide, seldom produces definite AKI. Similar results were reported by Hwang et al. in a cohort of 26 children with congenital heart disease undergoing cardiac catheterization [23]. Khatami et al. [24] used the same criteria for CI-AKI as we did, and recorded 5.8% of patients had CI-AKI when defined as an increase of more than 0.3 mg/dL in baseline SCr, and they found a much higher incidence of AKI patients when AKI was diagnosed by a 25% increase in base sCr. In our study, which was performed on children with normal renal function, no significant changes in serum cystatin C levels were detected at 24 hours or at 48

| Variables          | Baseline | 4 h after procedure | 24 h after procedure | 48 h after procedure | p     |
|--------------------|----------|---------------------|----------------------|----------------------|-------|
| Creatinine(μmol/l) | 66.5±18.0| nm                  | 71.4±19.3*           | 69.6±18.7*           | 0.009 |
| Cystatin C(mg/l)   | 0.76±0.18| nm                  | 0.77±0.17            | 0.76±0.15            | ns    |
| sNGAL(ng/ml)       | 49.2±15.8| nm                  | 51.7±13.3            | 48.7±16.2           | ns    |
| uNGAL(ng/ml)       | 10.35    | (8.8,5)             | 9.7 (66,9)           | 8.7 (93.7)           | 10.6 (67,0) ns |
| uKIM-1 (pg/ml)     | 236.2 (273.0) | 180.5 (245.5) | 320.8 (189.7)*#**   | 294.3 (204.4)**     | 0.006 |
| uKIM-1/uCr(pg/mg)  | 230.0 (273.3) | nm                  | 245.5 (204.61)      | 279.5 (293.9)*      | 0.007 |

sNGAL and uNGAL – serum and urinary neutrophil gelatinase-associated lipocalin; uKIM-1 – urinary kidney injury molecule-1; uKIM-1/uCr – KIM-1/creatinine ratio in spot urine; nm – not measured. * p<0.05 vs. 0h, ** p<0.05 vs. 4h; # p<0.01 vs. 4 h.

![Figure 1](image1.png)

Figure 1. Urinary KIM-1 changes after two different contrast media exposure during time; * p<0.05 vs. baseline; ** p<0.05 vs. 4 hours; # p<0.01 vs. 4 hours.

Table 4. ROC analysis of biomarkers’ diagnostic accuracy in early detection of CI-AKI.

| Value                | AUC (95% CI) | p value | Cut off | Sensitivity (95% CI) | Specificity (95% CI) |
|----------------------|--------------|---------|---------|----------------------|----------------------|
| sNGAL (ng/ml)        | 0.613 (0.473–0.754) | 0.353   | 55.4    | 83.3                 | 55.4                 |
| uNGAL (ng/ml)        | 0.512 (0.335–0.688) | 0.925   | 5.25    | 83.3                 | 30.8                 |
| uNGAL/uCr (ng/mg)    | 0.553 (0.367–0.739) | 0.663   | 7.03    | 66.7                 | 40.4                 |
| uKIM-1 (pg/ml)       | 0.495 (0.306–0.683) | 0.965   | 241     | 83.3                 | 38.2                 |
| uKIM-1/uCr (pg/mg)   | 0.757 (0.629–0.885) | 0.035   | 214     | 83.3                 | 54.2                 |

sNGAL and uNGAL – serum and urinary neutrophil gelatinase-associated lipocalin; uKIM-1 – urinary kidney injury molecule-1; uNGAL/uCr – NGAL/creatinine ratio in spot urine; uKIM-1/uCr – KIM-1/creatinine ratio in spot urine.
hours after administration of either contrast agent. This finding is the opposite of other studies where adult patients with chronic kidney disease were evaluated after coronary angiographies [25,26]. In 2007, Hirsch et al. were the first authors to report that elevation of NGAL in the serum and urine of children who had undergone a cardiac catheterization using a CM can be a predictive factor for CI-AKI [11]. In our study, there was no significant initial rise in urinary NGAL levels four hours after exposure to either of the two CM. We suppose that the difference in our ICM patient group arose from the presence of very few patients presenting definite CI-AKI, because we used a lower amount of contrast, and had no patients with cyanotic heart disease, compared to the previous study [11]. Therefore, here we can postulate, like Hwang et al., that NGAL, as very sensitive marker of ischemic AKI, has some limitations when it comes to diagnosing subclinical AKI developed from the use of contrast in children. This could also provide an explanation for our results as the patients were not on CPB; hence, ischemia as a trigger in NGAL synthesis was not excluded, while NGAL as marker of direct tubular toxicity has later sensitivity compared with ischemic conditions. Also, in a study by Oğuz et al., serum NGAL levels in addition to other novel biomarkers of AKI (N-acetyl-glucosaminidase, NAG, and cystatin C) were similar in adult patients at high risk for AKI after gadopentetate dimeglumine-enhanced MRI and MRI without contrast agent [27]. The authors showed that there was no adverse effect of magnetic field and/or gadopentetate dimeglumine (0.2 mmol/kg) on early acute renal injury biomarkers in this group of patients. In our study, at 24 hours post-Gd-DTPA exposure, serum NGAL was closely associated with creatinine and cystatin C, (\(t_r=0.498, p<0.001\); \(t_r=0.353, p=0.008\) respectively). These findings are in agreement with those of the other study after iodine-based contrast applications [25]. To date, subclinical nephrotoxicity has not been clearly defined. Akrawinthawong et al. defined subclinical AKI by a twofold or greater increase in NGAL and showed that 11.1% of patients with CKD undergoing coronary angiography with ICM developed subclinical AKI, in addition to 12.7% who were diagnosed with standard CI-AKI [28]. Similar to Khatami et al. [24], in our study we used an increase in novel biomarkers of 25% or more from baseline as indicative of subtle structural changes in the kidney (subclinical) after CM exposure. Regarding serum NGAL, after 24 hours we found this increase in the iopromide group in 32.6% of the patients and in 25.45% of the patients in the Gd-DTPA group. The average percent of sNGAL increase of the two subgroups of patients with sNGAL level more than 25% was significantly higher than the iopromide group (62.23%) than in the Gd-DTPA group (36.44%) (p=0.002). In a study by Akdeniz et al., uKIM-1 was a useful marker for the early diagnosis of CI-AKI in a group of 3,200 patients who had undergone coronary angiography. In their study, urinary KIM-1 levels increased significantly in patients with CI-AKI at the six-hour mark when compared with baseline [29]. In our study, we showed that KIM-1 excretion at 24 hours and urinary normalized KIM-1 at 48 hours were significantly higher than the baseline values in the group of children who were given gadolinium (Table 3), as opposed to the group of children who received ICM (Table 2). The receiver characteristic curve (ROC) analysis (Table 4, Figure 2) showed that normalized uKIM-1, 24 hours after exposure, was a better predictive factor for AKI than other biomarkers (AUC 0.757, cut off 214 pg/mg, sensitivity 83.3%, specificity 54.2%, p=0.035). Also, in a study by Duan et al., logistic regression analysis showed that urinary KIM-1 and IL-18 at 24 hours after gadolinium injection were independent predictive markers of Gd-CI-AKI [22]. The significant rise in uKIM-1 and normalized uKIM-1 at 24 hours and 48 hours after gadolinium application as well as its potentially predictive value for CI-AKI in our study were an interesting finding and requires further research in a larger sample of children. This ability to measure these novel biomarkers suggests a new frontier in the diagnosis of AKI and its consequences in terms of prevention and therapeutic strategies. Data relevant to prevention, such as N-acetylcysteine and/or bicarbonate infusion, furosemide [30], probucol [31], and others should be carefully evaluated in light of these new criteria. Further analysis is needed to show whether a gadolinium-based contrast agent is really much safer than iodinated-based media, even in children with normal renal function. The main limitation of this current study was the small size of the study population.

Conclusions

The use of gadopentetate dimeglumine (0.20 mL/kg), as well as with the application of iodinated-contrast media, in a group
of children with normal renal function might lead to subclinical nephrotoxicity. Serum NGAL and urinary KIM-1 need further evaluation as potential subclinical biomarkers of CI-AKI after iodinated-based and gadolinium-based CM administration, respectively. Normalized urinary KIM-1 could be one of the most useful non-invasive markers in detecting CI-AKI after iodine-based and gadolinium-based media exposure.

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