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Can serum Neutrophil Gelatinase Associated Lipocalin and Kidney Injury Molecule–1 help in decision making for surgery in antenatally dedected hydronephrosis

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Summary

Introduction
Congenital obstructive uropathies are among leading reasons for renal failure in children. Answers to questions such as what the critical threshold of obstruction is or which degree of obstruction disrupts the development of the kidney still remain unclear. Several biomarkers such as Kidney Injury Molecule 1 (KIM-1) and Neutrophil Gelatinase Associated Lipocalin (NGAL) may help clinicians in the clinical evaluation and appropriate planning of the disease.

Objective
This study aimed to investigate whether serum and urinary KIM-1 and NGAL levels contribute to conventional methods in decision-making for surgery in the postnatal period of infants with antenatal hydronephrosis.

Study design
34 patients with the diagnosis of antenatal hydronephrosis were evaluated prospectively. Renal pelvis diameters of all patients were above 10 mm in the ultrasonography (USG). Patients underwent diuretic renal scintigraphy after neonatal period. Patients were divided into two groups as surgery or follow-up based on USG and scintigraphy findings. Blood and urine samples were collected at first visits in both groups and again at the 3. Postoperative month in the surgery group. Serum and urinary NGAL and KIM-1 levels were measured by ELISA method. Study data were compared through the Mann–Whitney U and Wilcoxon Signed-Ranks test.

Results
There were 10 patients in the surgery group and 24 patients in the follow-up group. The age and gender did not differ between the groups. The surgery group had significantly higher median serum NGAL values (259.2 ng/mL) than that in the follow-up group (46.8 ng/mL, $p = 0.028$). The postoperative reduction of the median serum NGAL to 68.1 ng/mL compared to preoperative level was also found to be significant ($p = 0.037$) in the surgery group. Between the groups and within the surgery group no statistically significant difference was detected in terms of median urinary NGAL, and serum and urine KIM-1 levels.

Discussion
USG and renal scintigraphy are frequently used in determining whether patients with antenatal hydronephrosis need surgical intervention in the postnatal period. Several new biomarkers might help clinicians in decision making for surgery. KIM-1 and NGAL levels can be measured both in urine and serum. To our knowledge, this is the only study where serum NGAL and KIM-1 levels were measured in patients with antenatal diagnosis. Small sample size, lack of long term findings and control group are limitations of our study.

Conclusion
Serum NGAL levels of patients with antenatal hydronephrosis may help in decision making on the surgical intervention.

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Summary Table Comparison of the surgery and follow-up groups in terms of serum and urinary NGAL and KIM-1 values.

		Surgery group	Follow-up group	*P*
NGAL (ng/mL) median (IQR)	*Serum*	259.2 (43.1—394.8)	46.8 (33.7—69.9)	***0.028***
	Urine	5.9 (1.1—14.0)	2.1 (1.3—23.7)	*0.450*
KIM-1 (pg/mL) median (IQR)	*Serum*	3.9 (2.9—612.5)	2.6 (1.9—174.9)	*0.226*
	Urine	166.4 (18.3—439.8)	37.9 (12.1—190.1)	*0.385*

IQR: Interquartile range (25%—75%).

Introduction

The structural changes induced by congenital obstruction in the urinary system are classified as obstructive uropathy. Congenital obstructive uropathies are among leading reasons for renal failure and renal parenchymal injury secondary to restricting potential functions of the developing kidneys in infants and children [1,2]. The number of infants diagnosed with congenital obstructive uropathy has increased with the widespread use of antenatal ultrasonography (USG) [3]. Ureteropelvic junction (UPJ) obstructions is the most common obstructive cause of hydronephrosis detected in the antenatal period. Other important obstructive factors that lead to postnatal urinary tract damage include ureterovesical junction (UVJ) obstructions and posterior urethral valve [4,5].

Although many factors are thought to be effective in the etiology of obstructive uropathy, the answers to questions such as what the critical threshold of obstruction is or which degree of obstruction disrupts the development of the kidney still remain unclear. Since these patients have likely to have renal impairment if remain untreated, there is still no consensus on when and which patient should undergo surgery to preserve renal functions [6]. Though used for postnatal diagnosis and workup, or timing of surgery, USG, radionuclide studies, blood and urine laboratory tests may be insufficient in the course of the urinary system obstructions and selection of treatment modality [7]. Conventional blood and urine markers used in the diagnosis and monitoring of various kidney diseases are neither sensitive nor specific [8]. Serum urea and creatinine values are commonly used for the determination of kidney function, but they are not sensitive markers of obstructive uropathy. In addition, these parameters show functional changes in glomerular filtration capacity, but may not show changes in case of kidney injury [9]. Therefore, it is thought that several biomarkers that are novel and easy to test will help clinicians in the clinical evaluation of the disease, the appropriate planning of treatment, and the selection of patients who are candidates for surgery. Transforming growth factor B1, monocyte chemotactic protein-1, endothelin-1, N-acetyl-B-glucosaminidase, and epidermal growth factor were reported to be such potential biomarkers to indicate urinary obstruction [7,10—14]. Apart from these, Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Injury Molecule 1 (KIM-1) are the two recently studied markers.

KIM-1 is a type 1 transmembrane glycoprotein containing immunoglobulin and mucin domains. It has been shown to be produced in proximal kidney tubules after nephrotoxic injury or kidney ischemia [8,15—17]. NGAL is a protein from lipocalin family and it is reported that it may be an indicator for several renal diseases [18—20]. There are also studies in the literature reporting that the levels of KIM-1 and NGAL increase in serum and urine levels in obstructive nephropathy, ischemia or kidney injury due to nephrotoxic agents [15,21,22].

Conventional methods may not be sufficient to decide on surgery in the postnatal period in patients with hydronephrosis detected in the antenatal period. Considering this situation, this study aimed to investigate whether serum and urinary KIM-1 and NGAL levels contribute to conventional methods in decision-making for surgery in the postnatal period of infants with antenatal hydronephrosis.

Materials and method

Following the approval of Mersin University Clinical Research Ethics Committee (Approval date and no: 06.09.2012—2012/298), 34 patients who applied to the Pediatric Surgery Clinic between 01.10.2012 and 31.01.2014 with the diagnosis of antenatal hydronephrosis and who accepted the study were evaluated prospectively. The families of the patients included in the study were informed about the study and informed consent was obtained.

Renal pelvis diameters were above 10 mm in the USGs performed after the 25th gestational week in the antenatal period and in the first USG in the postnatal period for all patients included in the study. The gender and age of the patients were recorded at the time of application. Those who had USG-documented hydronephrosis and/or hydroureteronephrosis in the postnatal period underwent either Tc-99m DTPA (diethylenetriamine pentaacetate) or Tc-99m MAG-3 (mercaptoacetyltriglycine) diuretic scintigraphy after neonatal period. Patients were divided into two groups as surgery or follow-up based on the renal parenchymal thickness and renal pelvis diameter measured by USG and differential renal function values calculated by diuretic renal scintigraphy. The team, consisted of pediatric surgeon, pediatric nephrologist and nuclear medicine specialist, decided either surgical intervention for those who had a strong suspicion for obstruction in these parameters or conservative follow-up who did not exhibit obstructive pattern in diuretic renal scintigraphy and who had low suspicion of obstruction on USG. Patients with spinal cord pathology such as spina bifida or meningocele/meningomyelocele and those with duplex collecting system anomalies were not included in the study.

Blood and urine samples were collected at first visits in both groups and at postoperative third month in the

surgery group to be stored until the day to be analyzed. The subjects who had erythrocytes or leukocytes in urine samples were further checked for any urinary tract infection and had their urinalysis repeated. All blood samples were centrifuged for 10 min at 4000 rpm to extract serum parts and urine samples were centrifuged at 3000 rpm for 5 min; both samples were stored −80 °C. These stored samples were analyzed after waiting until they reached room temperature on the study day. In this study, NGAL and KIM-1 levels were determined by ELISA method.

Serum and urine NGAL levels were analyzed on DSX™ Four-Plate Automated ELISA Processing System microELISA device (Dynex Technologies, Virginia, United States) using a Human Lipocalin-2/NGAL ELISA kit (BioVendor Research and Diagnostic Products, Czech Republic, LOT: E14-018) at 450 nm wavelength. The amount of NGAL in the samples was calculated according to the curve formed by the absorbance and concentrations of the standards. The lower measurement limit for the NGAL in the samples was 0.3 ng/mL, the upper measurement limit was 10 ng/mL (0.3 ng/mL, 0.6 ng/mL, 1.25 ng/mL, 2.5 ng/mL, 5 ng/mL, 10 ng/mL).

Serum and urine KIM-1 levels were tested on DSX™ Four-Plate Automated ELISA Processing System microELISA device (Dynex Technologies, Virginia, United States) via a SEA785Hu ELISA Kit For Kidney Injury Molecule 1 (Cloud-Clone Corp., United States, LOT: L140522455) at 450 nm wavelength. The amount of KIM-1 in the samples was calculated according to the curve formed by the absorbance and concentrations of the standards. The lower measurement limit for the KIM-1 in the samples was 78 pg/mL, the upper measurement limit was 5000 pg/mL (78 pg/mL, 156 pg/mL, 312 pg/mL, 625 pg/mL, 1250 pg/mL, 2500 pg/mL, 5000 pg/mL).

Statistical analysis

Datas were analyzed using NCSS (Number Cruncher Statistical System) 2007 software (Kaysville, Utah, United States). Study data were expressed by descriptive methods (mean, standard deviation, median, frequency, percentage, minimum, maximum). Non-normally distributed data were compared through the Mann−Whitney U test between the groups and through the Wilcoxon Signed-Ranks test to show within-group differences. Categorical variables were compared via Fisher's exact test. An overall 5% Type-I error level was used to infer statistical significance. Spearman's Rho Correlation analysis test was used to determine the relationship between serum NGAL level and renal pelvis diameter and differential renal function.

Results

The boys were found to constitute 85.3% (n = 29) of the study population, where the mean age was 4.9 ± 6.3 months (range: 1−36 months). The mean age was 4.9 ± 3.4 months (range: 2−12 months) in the surgery group and 4.9 ± 7.3 months (range: 1−36 months) in the follow-up group. The age and gender did not differ between the study groups. In the surgery group, mean value of anteroposterior renal pelvis diameters of the patients was 34,1 mm (range: 15−51). Mean value of differential renal function in the surgery group was 39.4% (range: 18%−45%). Demographic data, ultrasonographic and scintigraphic findings are shown in Table 1.

In the surgery group, dismembered pyeloplasty was performed in three patients (30.0%) due to right UPJ obstruction and in seven patients (70.0%) due to left UPJ obstruction, Hydronephrosis was detected in 87.5% of the follow-up patients, where 13 cases (54.1%) had left-sided presentation and eight cases (33.3%) with the right-side. In addition, three patients (12.5%) had hydroureteronephrosis (HUN), including one patient for each of the left-sided, right-sided, and bilateral presentation. Voiding cystography and dynamic diuretic renal scintigraphy was performed in patients with HUN to rule out reflux and obstruction. It was found that urinary system dilatations of the patients with HUN resolved and returned to normal during the follow-up (Fig. 1).

The surgery group had significantly higher median serum NGAL values at the time of admission (259.2 ng/mL) than that in the follow-up group (46.8 ng/mL, p = 0.028) (Fig. 2). These two groups were found to be similar in terms of the median urinary NGAL, and serum and urine KIM-1 levels (Table 2). Within the surgery group, the post-operative reduction of the median serum NGAL to 68.1 ng/mL compared to preoperative level was found to be significant (p = 0.037) (Fig. 2). No statistically significant difference was detected between preoperative and post-operative urinary NGAL, and serum and urine KIM-1 levels (Table 3).

According to the statistical analysis, cut off value for serum NGAL was found to be 124,35 ng/mL. The area under the curve was found to be 0.742. Specify of the test was 95.8% and sensitivity was 60% (Fig. 3).

Spearman's Rho correlation test was used to determine whether there is any correlation between preoperative serum NGAL levels and anteroposterior renal pelvis diameter and differential renal function. Test did not reveal any correlation between serum NGAL levels and renal pelvis diameter ($r = 0.154$; $p > 0.05$). Test also did not reveal any correlation between serum NGAL levels and differential renal function ($r = 0.590$; $p > 0.05$).

Table 1 Demographic data, ultrasonographic and scintigraphic findings of patients.

	Surgery group	Follow-up group
Gender		
Boys (n)	7 (70%)	22 (91%)
Girls (n)	3 (30%)	2 (9%)
Age	4.9 ± 3.4 months	4.9 ± 7.3 months
(mean)	(2−12)	(1−36)
APD[a]	34.1 mm	13.6 mm
(mean)	(15−51)	(10−21)
DRF[b]	39.4%	50.2%
(mean)	(18%−45%)	(45%−54%)

[a] Anteroposterior diameter of renal pelvis.
[b] Differential renal function.

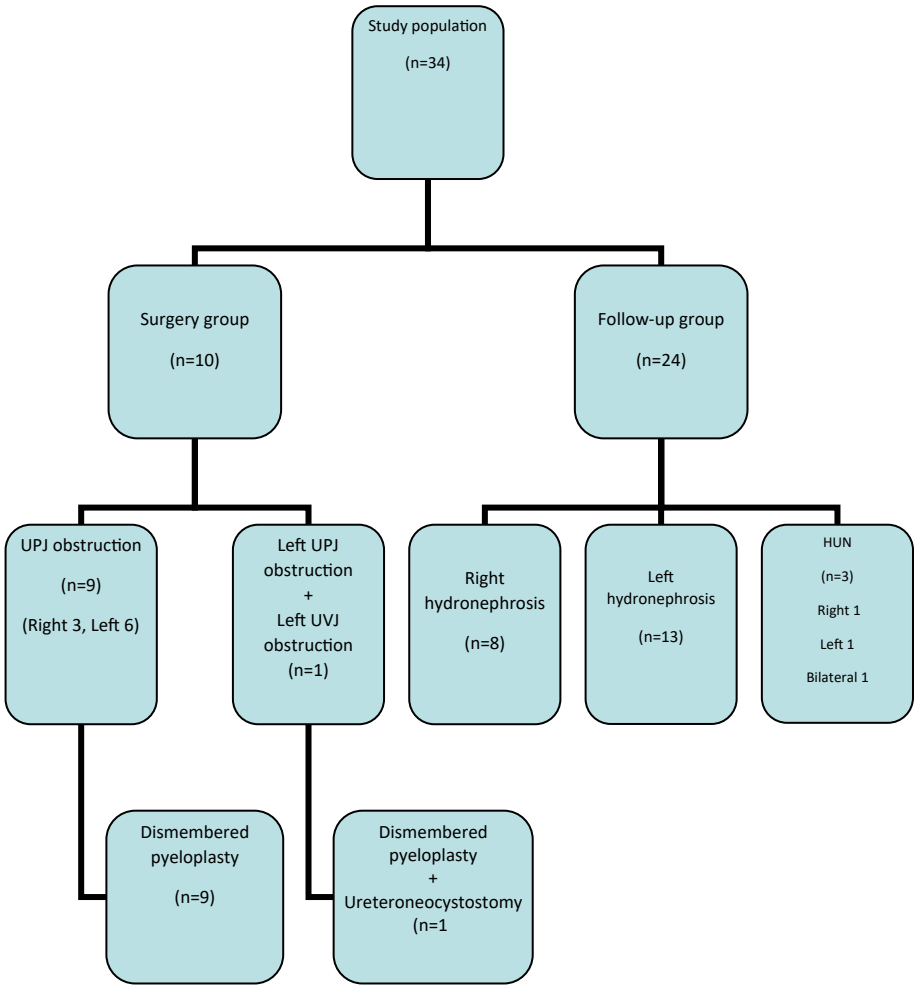

Fig. 1 Patient flow in the study groups with sides affected and numbers of the hydronephrosis or HUN. UPJ, ureteropelvic junction; UVJ, ureterovesical junction; HUN, Hydroureteronephrosis.

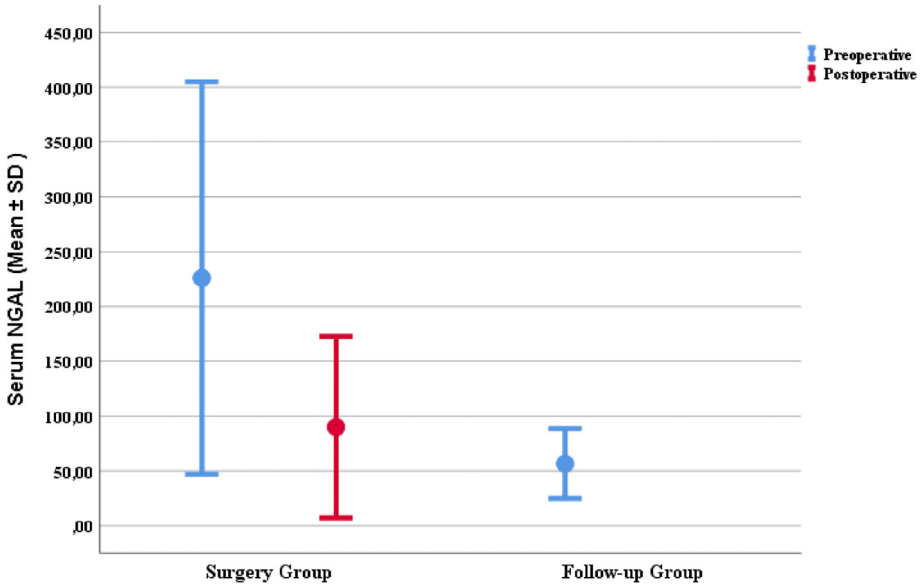

Fig. 2 Comparison of serum NGAL values in the surgery and follow-up groups. The preoperative and postoperative difference in the surgery group was statistically significant ($p < 0.05$); the difference between the groups was also statistically significant ($p < 0.05$).

Table 2 Comparison of the surgery and follow-up groups in terms of serum and urinary NGAL and KIM-1 values.

		Surgery group	Follow-up group	*P*
NGAL (ng/mL) median (IQR)	*Serum*	259.2 (43.1—394.8)	46.8 (33.7—69.9)	*0.028*
	Urine	5.9 (1.1—14)	2.1 (1.3—23.7)	*0.450*
KIM-1 (pg/mL) median (IQR)	*Serum*	3.9 (2.9—612.5)	2.6 (1.9—174.9)	*0.226*
	Urine	166.4 (18.3—439.8)	37.9 (12.1—190.1)	*0.385*

IQR:Interquartile range (25%—75% perc).

Table 3 Comparison of preoperative and postoperative serum and urinary NGAL and KIM-1 values in the surgery group.

		Preoperative	Postoperative	*P*
NGAL (ng/mL) median (IQR)	*Serum*	259.2 (43.1—394.8)	68.1 (46.2—95)	*0.037*
	Urine	5.9 (1.1—14)	2.1 (1.3—23.7)	*0.959*
KIM-1 (pg/mL) median (IQR)	*Serum*	3.9 (2.9—612.5)	9.8 (3.6—86.6)	*0.445*
	Urine	166.4 (18.3—439.8)	164.6 (20.2—883.7)	*0.285*

IQR:Interquartile range (25%—75% perc).

Discussion

In our study, patients with hydronephrosis in the antenatal period were grouped into two groups as those who underwent surgery and those who were followed up conservatively, and serum and urine NGAL and KIM-1 values were studied in both groups. NGAL and KIM-1 values were measured at the end of the study. In other words NGAL and KIM — 1 levels were not known prior to surgery.

The study by Cheng reported that, renal function in renography, enlarging of hydronephrosis, parenchymal thinning on ultrasonography, the follow-up protocol and family compliance are the indications for the surgical management [23]. We almost used same criteria in decision making for surgical intervention.

Serum NGAL level was found to be significantly increased in the surgery group while urinary NGAL and KIM-1 levels were also found to be higher, albeit not significant. Within the surgery group, the postoperative reduction of the median serum NGAL compared to preoperative level was found to be significant as well, but statistically significant difference was not detected between preoperative and postoperative urinary NGAL, and serum and urine KIM-1 levels.

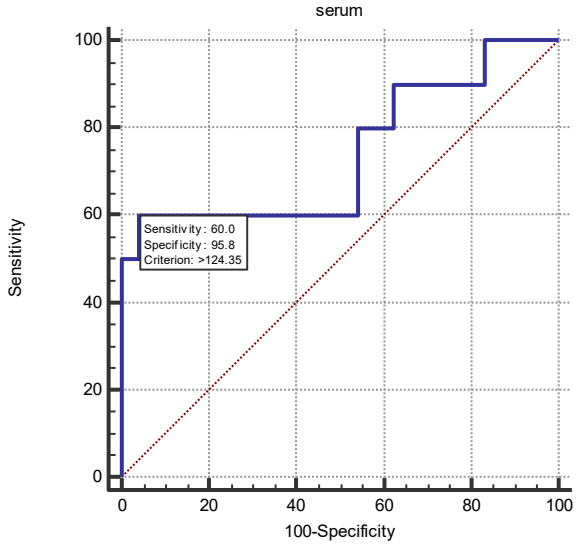

Fig. 3 ROC curve of Serum NGAL. Area under the curve was found to be 0.742.

Conservative follow-up has become more popular in the management of infants with hydronephrosis detected in the antenatal period. While approximately 35—50% of uropathy detected prenatally were UPJ obstruction, only %19—29 of them were reported to require surgical intervention [24,25].

Today, USG and dynamic renal scintigraphy studies are frequently used in determining whether there is obstruction in the urinary system in patients diagnosed with hydronephrosis in the antenatal period and to inform decision-making in case of obstruction [26]. However, these conventional methods might be inadequate for many patients and may lead to inappropriate decisions. Moreover, the optimal approach is to detect obstruction clinically and radiologically before the onset of renal injury and to administer appropriate treatment. This has caused the need for investigation of other novel methods. Advances in molecular diagnostic methods have brought the idea that several biomarkers may be useful to indicate renal injury associated with obstructive uropathy and to help with the decision-making process for the surgery.

KIM-1 which is a type 1 transmembrane glycoprotein containing immunoglobulin and mucin domains, was reported to involve in the remodeling phase after injury to renal tubules [16]. NGAL belongs to the lipocalin family of proteins and are secreted from various tissues [15]. Its level in urine was reported to have the potential to be a biomarker for several diseases, including acute renal failure, diabetic nephropathy, IgA nephropathy, and contrast-induced nephropathy [18—20]. There are studies that reported both biomarkers to be associated with renal scarring in patients with vesicoureteral reflux. The study by Parmaksiz et al. reported that urinary NGAL might be a diagnostic biomarker in predicting renal scarring secondary to

reflux nephropathy [27]. Another study by Toker et al. reported urinary KIM-1 to be non-invasive biomarker to indicate renal scarring in patients with vesicoureteral reflux [28].

The study by Kostic et al., who investigated several biomarkers in infants with antenatal hydronephrosis and suspected urinary obstruction, reported a dramatic postoperative reduction of all biomarkers tested, especially of urinary NGAL [29]. Karakus et al. compared patients with antenatal diagnosis of hydronephrosis and postnatal detection of UPJ obstruction with a healthy control group to investigate several biomarkers. The authors reported that urinary NGAL levels started to diminish at postoperative period yet could reach to the level observed in healthy children only at three years from the surgery [30]. Similarly, we observed that urinary NGAL values tended to decline at the postoperative third month in our study.

The study by Pavlaki et al. reported significant difference between preoperative and postoperative urinary NGAL levels in 22 infants, where the latter measurement was performed after 12 months from the surgery [6]. Moreover, Wasilewska et al. conducted a similar study and reported a reduction in urinary NGAL levels at postoperative third month [15]. We also observed a trend to decreased NGAL levels postoperatively but not reaching statistical significance. This might be partly explained by our smaller sample size and lack of long-term urinary NGAL levels, considering available findings in the above-mentioned studies.

Our study showed a numerical increase of serum and urinary KIM-1 levels in the surgery group compared to the conservative approach. Within the surgery group, median serum KIM-1 level was higher in the postoperative measurement compared to baseline whereas urinary KIM-1 level was very similar. Consistently, the study of Wasilewska et al. reported no difference between the urinary KIM-1 level measured preoperatively and at postoperative third month [15]. Karakus et al. reported urinary KIM-1 levels to be higher in both surgery and follow-up groups than that in the healthy subjects and no difference of urinary KIM-1 at third month but significant decline at sixth month after the surgery [29]. The role of KIM-1 in remodeling may explain the fact that KIM-1 values remained still elevated at postoperative third month [21]. We believe that later measurements of the urinary and serum KIM-1 levels after the surgery may be different. While the studies in the literature reported serum levels of several biomarkers, only the urinary levels of NGAL and KIM-1 was investigated [6,15,29,30]. To our knowledge, this is the only study where serum NGAL and KIM-1 levels were measured in patients with antenatal diagnosis.

Our study has several limitations. We have a smaller sample size and compared to those in the literature and we don't have a control group. In addition, we only measured levels at third month after the surgery, lacking long-term findings. We believe that statistically strong conclusions could be drawn with studies having larger number of study population and a longer duration of follow-up.

Conclusion

In conclusion, conservative follow-up has become the mainstay approach in children with antenatal hydronephrosis in recent years. We suggest that serum NGAL level of patients, who are candidates for surgery, may help in decision making on the surgical intervention. Further studies with larger series are needed to make such biomarkers available in clinical practice.

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Ethical approval

This study is approved by Mersin University Clinical Research Ethics Committee.

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Conflicts of interest

No conflict of interest has been declared by the authors.

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Dogakan Yigit: Planning and writing the study. Hakan Taskinlar: Writing assistance. Dincer Avlan: Planning the study, proof reading.

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