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ORIGINAL ARTICLE

Urinary neutrophil gelatinase-associated lipocalin as a biomarker to monitor renal function in patients with obstructive ureteral calculi

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Abstract

Purpose Our study aimed to investigate the clinical significance of urinary neutrophil gelatinase-associated lipocalin (NGAL) as an effective real-time monitoring biomarker of renal function in patients with obstructive ureteral calculi presenting renal colic.

Methods A cohort of 89 first-visit patients with renal colic caused by unilateral ureteral calculi were retrospectively reviewed. 46 of which received double-J ureteral stent placement (group 1) and the remaining 43 treated conservatively with analgesics and hydration (group 2) when diagnosed. Urinary NGAL (uNGAL) values in the baseline, 2 h and 1 day after treatments were recorded. The variation of this parameter over time and the association with patients' characteristics were analyzed.

Results uNGAL levels decreased as time went by for patients receiving double-J ureteral stent placement (47.23 ± 28.32 ng/mL for baseline, 40.73 ± 21.86 ng/mL for 2 h and 34.67 ± 18.00 ng/mL for 1 day after operation; $p = 0.0363$). Nevertheless, for those treating conservatively, the levels emerged a mild increase (50.63 ± 32.30 ng/mL, 56.00 ± 32.01 ng/mL and 60.63 ± 34.08 ng/mL, correspondingly; $p = 0.3708$). By analyzing the association between uNGAL variation and patients' characteristics of group 1, operation duration showed the best correlation coefficient (Pearson $r = 0.6106$, $r^2 = 0.3728$, $p < 0.0001$).

Conclusions uNGAL can be used as a biomarker to monitor the renal function effectively when serum creatinine (sCr) was within normal limits. And double-J ureteral stent can be considered as a protective factor to renal function in patients with obstructive ureteral calculi presenting renal colic.

Keywords Acute kidney injury (AKI) · Double-J ureteral stent · Neutrophil gelatinase-associated lipocalin (NGAL) · Renal colic · Ureteral calculi

Abbreviations

AKI	Acute kidney injury
ANOVA	Analysis of variance
CKD	Chronic kidney disease
CPB	Cardiopulmonary bypass
CT	Computerized tomography
Cys-C	Cystatin C
ESWL	Extracorporeal shock wave lithotripsy
KIM-1	Kidney injury molecule-1
L-FABP	Liver-type fatty acids binding protein
NGAL	Neutrophil gelatinase-associated lipocalin
NRS	Numerical rating scale
ROC	Receiver operating characteristics
sCr	Serum creatinine
SD	Standard deviation
sNGAL	Serum NGAL
uNGAL	Urinary NGAL
URL	Ureteroscopic lithotripsy
URS	Ureterorenoscopy
UTI	Urinary tract infection

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Introduction

Double-J ureteral stent is an urgent but temporary urologic procedure used to manage patients with hydronephrosis accompanying with acute kidney injury (AKI) caused by ureteral calculi. For those patients, early intervention is the most important matter for protecting renal function, which depends on early detection of renal injury. It is well known that the diagnosis of AKI relies mainly on serum creatinine (sCr) kinetic monitoring. Unfortunately, sCr elevation is a late indicator of acute changes in renal function, because of a 24–48 h delay between renal insult and significant sCr elevation [1]. Recently, some biomarkers have been recommended with the ability to better identify renal damage in the early phase compared with traditional markers. The focus has mainly been on markers like neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C (Cys-C) and liver-type fatty acids binding protein (L-FABP) [2]. Among those increasing rapidly after a renal insult, NGAL is of particular interest and has even been considered as a "renal troponin" [3].

NGAL was purified from the secondary granules of human neutrophils for the first time in the early 1990s [4, 5]. And several studies have shown encouraging results of urinary NGAL (uNGAL) for early detection of AKI in different clinical settings [6–10]. NGAL fulfills many characteristics for an ideal biomarker for AKI. (1) It is rapidly induced and released from the injured distal nephron in experimental models and human disease [11–13]. As reported, increases in NGAL levels predict AKI 24–72 h before diagnostic sCr increases [7, 8, 11, 14–16] and are of prognostic value [17] in response to renal injury. (2) Its urine and plasma concentrations increase proportionally to severity and duration of renal injury [12, 14, 15]. (3) Its concentration rapidly decreases with attenuation of renal injury [18]. (4) It is readily and easily measured in plasma [14] and urine [15]. And its urine concentration is an almost perfect AKI predictor with an area under the receiver operating characteristics (ROC) curve of 0.998 [19]. And its predictive values increase when NGAL is measured closer to the time of insult [20].

AKI is subclassified into pre-renal, intra-renal and post-renal forms. This discrimination of different origins of kidney injury is important because urologists concern more about the postrenal AKI. Urbschat et al. found high levels of serum NGAL (sNGAL) and uNGAL were observed in stone-induced acute obstructive nephropathy, representing a valuable marker of postrenal AKI [21]. Benli et al. discovered that there was an important change in NGAL after the ureterorenoscopy (URS) procedure [22]. All those findings indicated NGAL a potential surrogate marker of acute postrenal kidney injury.

From these viewpoints, we have investigated the clinical significance of uNGAL as an effective real-time monitoring biomarker of renal function variation, and evaluated uNGAL as a potential surrogate biomarker for providing early intervention of double-J ureteral stent placement in patients with ureteral calculi presenting renal colic.

Methods

Study design

This was a retrospective study conducted on patients diagnosed with urolithiasis in Xinhua Hospital who bothered with ureteral calculi presenting the first episode renal colic. All those objects corresponded to the following conditions. (1) A noncontrast computerized tomography (CT) scan or ultrasound inspection proved an unilateral ureteral calculi larger than 6 mm; (2) sCr was within normal limits and without disturbance of acid–base balance of water and electrolytes when diagnosed; (3) receiving double-J ureteral stent placement or treating conservatively with analgesics and hydration as treatment methods (For all those patients, following treatment like extracorporeal shock wave lithotripsy (ESWL) or ureteroscopic lithotripsy (URL) etc should been implemented). The exclusion criteria were: (1) with history of urolithiasis, hydronephrosis or chronic kidney disease (CKD); (2) medical history of manual or instrumental urological intervention; (3) medical history of cardiopulmonary bypass (CPB); (3) sepsis or urinary tract infection (UTI); (4) single kidney; (5) pregnancy; (6) immunodeficiency; (7) with any malignant diseases; (7) with evidence of acute exacerbations of obstructive pulmonary; (8) incomplete medical data or the remaining biological samples was not enough for reanalyzing [23].

A total of 89 patients from July 2016 to December 2017 were reviewed. Patients were divided into two groups. Those receiving double-J ureteral stent placement were assigned to group 1 and the remaining treating conservatively with analgesics and hydration were distributed to group 2. Detailed information of age, gender, pain intensity evaluating by numerical rating scale (NRS), description of calculi (including the location, maximum diameter, etc.) and hydronephrosis evaluated by noncontrast CT scan or ultrasound was recorded. All the biological samples reanalyzed for sCr and uNGAL in this study were from the remaining portion of the conventional clinical usage, which were stored at – 80 °C.

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Xinhua Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Urinary NGAL measurement

Midstream urine was utilized to analysis uNGAL. uNGAL level was determined using a commercially available enzyme-linked immunosorbent assay kit (Human Lipocalin-2/NGAL DuoSet DY1757, R&D Systems, Minneapolis, MN, USA). For detection of uNGAL, urine was diluted 1:50. All measurements were taken in duplicate and in strict accordance with the protocal. The optical density of the colour-forming substrate tetramethylbenzidine was determined at 450 nm using a microplate reader (DigiScan Photometer, ASYS Hitech, Eugendorf, Austria).

Statistical analysis

Statistical comparisons were performed using the statistical software GraphPad Prism 5. Continuous variables were expressed as mean ± standard deviation (SD). The intergroup differences were tested using the Student's *t* test or analysis of variance (ANOVA). Categorical variables were expressed as frequency (percentage), and Chi square test was used to test the intergroup differences. Pearson correlation analysis was used to analyze the interdependency between variables. Statistical significance was defined as a $p < 0.05$.

Results

Demographic data

46 patients receiving double-J ureteral stent placement were classified into group 1, and 43 patients treating conservatively with analgesics and hydration were classified into group 2. Patients of both groups did not significantly differ in age, gender, calculi maximum diameter, calculi location, hydronephrosis, pain intensity, sCr and uNGAL when enrolled. All demographic characteristics of the 89 patients are listed in Table 1.

Analysis of sCr variation

sCr levels of patients receiving double-J ureteral stent placement were identified as 80.62 ± 13.19 μmol/L for baseline, 75.72 ± 18.22 μmol/L for 2 h, and 75.85 ± 13.95 μmol/L for 1 day after operation. sCr did not change obviously after placing the double-J ureteral stent by comparing with the baseline ($p = 0.1524$). The variation in sCr levels of patients treated conservatively with analgesics and hydration was similar; 78.86 ± 12.00 μmol/L, 78.24 ± 13.39 μmol/L and 80.71 ± 14.53 μmol/L, correspondingly ($p = 0.6714$) (Table 2). Meanwhile, patients of both groups did not significantly differ in sCr levels for the baseline, 2 h and 1 day post-treatment as well (Fig. 1).

Table 1 Characteristics of the study population

	Total	Group 1	Group 2	*p* value
Number	89	46	43	–
Mean (SD) age (years)	49.3 (14.2)	49.6 (2.2)	48.9 (2.0)	0.8224†
Gender				0.838‡
Female (%)	26 (29.21)	13 (28.26)	13 (30.23)	–
Male (%)	63 (70.79)	33 (71.74)	30 (69.77)	–
General calculi location				0.865‡
Right (%)	36 (40.45)	19 (41.30)	17 (39.53)	–
Left (%)	53 (59.55)	27 (58.70)	26 (60.47)	–
Detailed calculi location				0.585‡
Upper ureter (%)	46 (51.68)	25 (54.35)	21 (48.84)	–
Middle ureter (%)	30 (33.71)	16 (34.78)	14 (32.56)	–
Lower ureter (%)	13 (14.61)	5 (10.87)	8 (18.60)	–
Mean (SD) calculi maximum diameter (cm)	0.816 (0.153)	0.838 (0.158)	0.794 (0.146)	0.1719†
Mean (SD) sCr (μmol/L)	79.77 (12.59)	80.62 (13.19)	78.86 (12.00)	0.5127†
Mean (SD) hydronephrosis (mm)	11.2 (9.3)	10.4 (9.1)	12.2 (9.6)	0.3549†
Mean (SD) pain intensity	6.2 (1.7)	6.2 (1.7)	6.3 (1.7)	0.7703†
Mean (SD) uNGAL (ng/mL)	48.87 (30.18)	47.23 (28.32)	50.63 (32.30)	0.5985†

Values are in mean (SD) or *n* (%)

SD standard deviation, *sCr* serum creatinine, *uNGAL* urinary neutrophil gelatinase-associated lipocalin

†Student's *t* test

‡Chi square test

Table 2 Analysis of sCr in the baseline and after treatments in both groups

	Baseline (μmol/L)	2 h post-treatment (μmol/L)	1 day post-treatment (μmol/L)	*p* value
Group 1	80.62 (13.19)	75.72 (18.22)	75.85 (13.95)	0.1524[†]
Group 2	78.86 (12.00)	78.24 (13.39)	80.71 (14.53)	0.6714[†]

Values are in mean (SD)

SD standard deviation, *sCr* serum creatinine

[†]ANOVA

Analysis of uNGAL variation

NGAL values measured in urine of patients receiving double-J ureteral stent placement were identified as 47.23 ± 28.32 ng/mL for baseline, 40.73 ± 21.86 ng/mL for 2 h, and 34.67 ± 18.00 ng/mL for 1 day after operation. The uNGAL levels decreased obviously after placing the double-J ureteral stent and the variation in uNGAL was statistically significant ($p = 0.0363$). Post-test showed that the significant difference occurred only when 1 day after operation compared to the baseline. However, the variation in uNGAL of patients treating conservatively did not change remarkably; 50.63 ± 32.30 ng/mL, 56.00 ± 32.01 ng/mL and 60.63 ± 34.08 ng/mL, correspondingly. Though there was a slight increase in uNGAL during this period compared to the baseline, this increase did not reach statistical significance ($p = 0.3708$) (Table 3).

Table 3 Analysis of uNGAL in the baseline and after treatments in both groups

	Baseline (ng/mL)	2 h post-treatment (ng/mL)	1 day post-treatment (ng/mL)	*p* value
Group 1	47.23 (28.32)	40.73 (21.86)	34.67 (18.00)[‡]	0.0363[*†]
Group 2	50.63 (32.30)	56.00 (32.01)	60.63 (34.08)	0.3708[†]

Values are in mean (SD)

SD standard deviation, *uNGAL* urinary neutrophil gelatinase-associated lipocalin

[†]ANOVA

[‡]Post-test of ANOVA showing statistical significance compared to baseline

[*]Statistical significance ($p < 0.05$)

While patients of both groups did not significantly differ in uNGAL levels in the baseline, the difference came up to statistically significant when 2 h and 1 day after treatment. The uNGAL levels of 2 h after treatment for group 1 and group 2 were 40.73 ± 21.86 ng/mL and 56.00 ± 32.01 ng/mL ($p = 0.0098$), respectively. And the uNGAL levels of 1 day after treatment were 34.67 ± 18.00 ng/mL and 60.63 ± 34.08 ng/mL ($p < 0.0001$), respectively (Fig. 1).

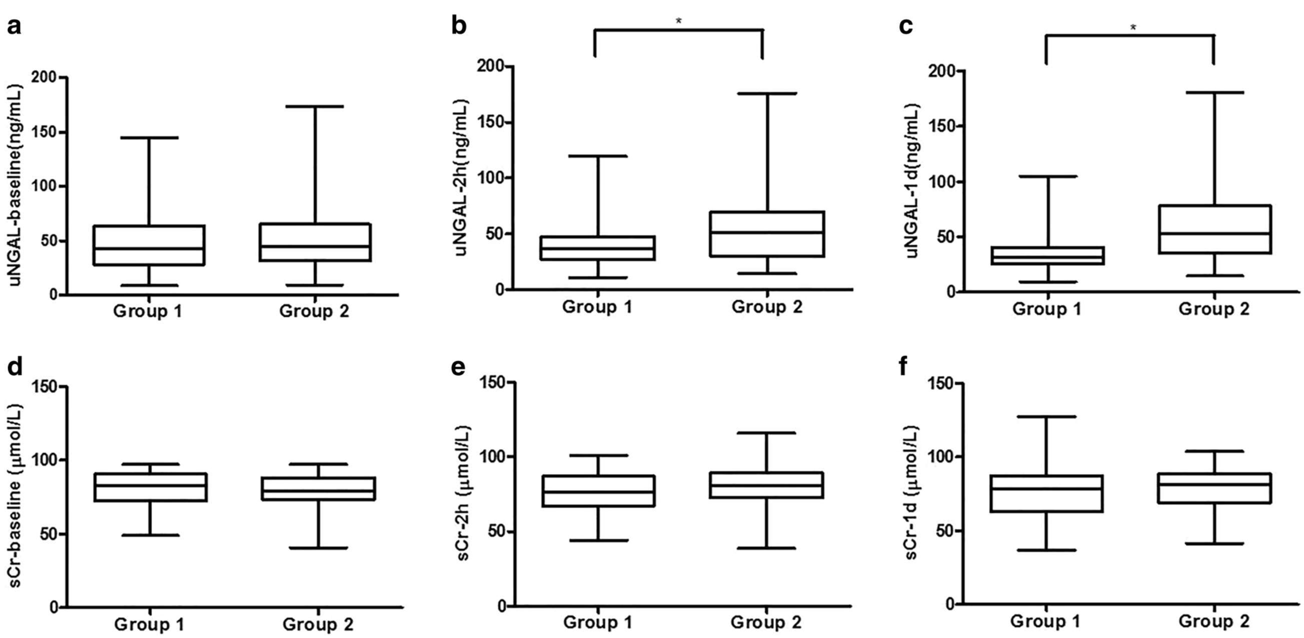

Fig. 1 Analysis of sCr and uNGAL variation in group 1 and group 2. **a**–**c** uNGAL in the baseline, 2 h and 1 day after treatment, respectively; **d**–**f** sCr in the baseline, 2 h and 1 day after treatment, correspondingly. *$p < 0.05$, were assumed as statistically significant. *sCr* serum creatinine, *uNGAL* urinary neutrophil gelatinase-associated lipocalin

Influence factors of uNGAL variation after double-J ureteral stent placement

Furthermore, the relationship between uNGAL change rate and demographic characteristics of group 1 patients were analyzed (age, gender, calculi maximum diameter, calculi location, sCr at baseline, hydronephrosis, pain intensity, uNGAL at baseline, operation duration, etc.). Student's *t* test was used for gender and general calculi location (left or right); ANOVA was used for pain intensity and detailed calculi location (upper, middle or lower ureter) to estimate the interdependency with uNGAL variation. Results showed that there was no statistically significant interdependency among those other than the detailed calculi location (Table 4). We found that when the calculi were located in the lower ureter, the uNGAL levels increased instead of decreasing 1 day after surgery. There was statistically significant difference when compared to the middle ureter. That was to say the location of calculi influenced the therapeutic effect indeed. Consequently, it seemed not a good solution for patients with lower ureteral calculi presenting renal colic to receive a double-J ureteral stent placement. But to be interesting, all the patients with lower ureteral calculi were all females and had smaller calculi size (0.632 ± 0.029 cm vs. 0.838 ± 0.158 cm; $p = 0.0058$). However, there were no distinguished differences in the severity of hydronephrosis (8.4 ± 4.9 mm vs. 10.4 ± 9.1 mm; $p = 0.6405$), sCr (79.36 ± 14.94 µmol/L vs. 80.62 ± 13.19 µmol/L; $p = 0.8419$), uNGAL (34.86 ± 17.06 ng/mL vs. 47.23 ± 28.32 ng/mL; $p = 0.3453$), and operation duration (7.2 ± 5.7 min vs. 6.5 ± 4.2 min; $p = 0.7328$) as compared to the mean value of the total patients in group 1. Unfortunately, the persuasion of this result was limited because of the very limited sample capacity (only five patients in this study) of patients with lower ureteral calculi.

In addition, Pearson correlation analysis was used to analyze the interdependency between uNGAL change rate and patients' continuous demographic characteristics. Among those characteristics, only hydronephrosis, uNGAL and operation duration [mean (SD): 6.5 (4.2) min] had statistically significant interdependency with uNGAL variation (Pearson $r = -0.3448, -0.5443, 0.6106$; $r^2 = 0.1189, 0.2962, 0.3728$; with $p = 0.0190, < 0.0001, < 0.0001$, respectively) (Fig. 2). As showed above, operation duration had the highest correlation coefficient with uNGAL change rate, meaning the shorter operation time, the more uNGAL would decrease after surgery.

Discussion

Urolithiasis is a relatively common condition in different continents and countries. Patients presenting with renal colic in the emergency room can often be treated conservatively with analgesics and hydration. In some cases with obstructive ureteral calculi causing intractable pain or pyuria, more urgent intervention might be necessary (i.e., with antibiotics and decompression of the obstruction to avoid sepsis) [24]. But how to deal with the patients whose sCr is within normal limits and without disturbance of acid–base balance of water and electrolytes, as well as no evidence of refractory pain, fever, or pyuria is still confused to urologists. As sCr requires several hours to days to accumulate, it increases in serum only after 50% or more of renal function is lost and its concentration is affected by multiple confounding factors [25]. Therefore, most episodes of subclinical AKI patients needing seasonable surgical intervention might be missed. Since AKI worsens renal but also overall prognosis, new biomarkers allowing for early detection and monitoring of AKI are eagerly awaited. Therefore, we investigated

Table 4 Correlation between uNGAL variation and patients' categorical demographic characteristics (gender, pain intensity and calculi location) of group 1 patients

	Gender		Pain intensity				General calculi location		Detailed calculi location		
	Female	Male	4	6	7	9	Right	Left	Upper	Middle	Lower
Mean (SD) uNGAL change (%)	− 17.25 (17.94)	− 20.97 (22.19)	− 23.56 (16.27)	− 18.51 (23.86)	− 16.32 (25.00)	− 22.45 (17.45)	− 13.23 (24.62)	− 24.62 (16.86)	− 20.73 (21.40)	− 25.45 (15.04)	1.85 (24.92)§
p value	0.5932†		0.8265‡				0.0689†		0.0339*,‡		

Values are in mean (SD)

SD standard deviation, *uNGAL* urinary neutrophil gelatinase-associated lipocalin

†Student's *t* test

‡ANOVA

§Statistical significance compared to the location of middle ureter

*Statistical significance ($p < 0.05$)

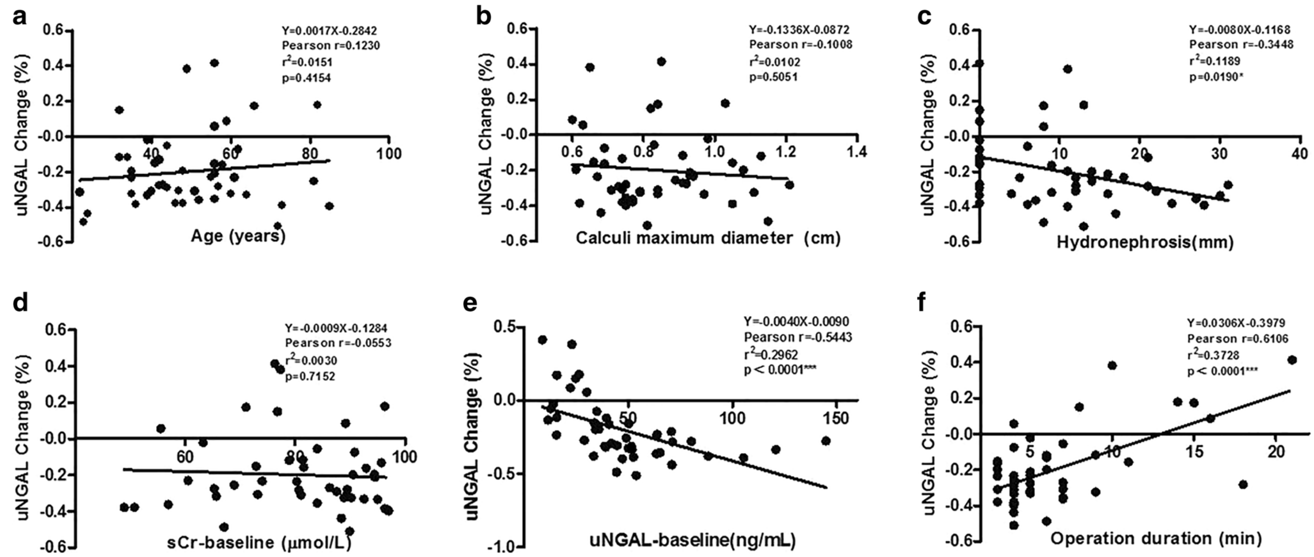

Fig. 2 Pearson correlation analysis of uNGAL variation and patients' continuous demographic characteristics of group 1. **a**–**f** Represented age, calculi maximum diameter, hydronephrosis, sCr in the baseline, uNGAL in the baseline, operation duration, correspondingly. $^*p<0.05$, $^{***}p<0.0001$, were assumed as statistically significant. *sCr* serum creatinine, *uNGAL* urinary neutrophil gelatinase-associated lipocalin

whether the most promising biomarker, namely uNGAL, might answer this need in the daily clinical practice.

The main findings of our trial are that: (1) uNGAL can be used as a biomarker to discover the status of kidney injury earlier and monitor the renal function variation effectively when sCr is within normal limits, as well as an efficacy evaluation indicator of different surgical or medical interventions, which may help to further understand the obstructive nephropathy. (2) Double-J ureteral stent placement is a protective factor to renal function in patients with obstructive ureteral calculi presenting renal colic. When patients with renal colic show the uNGAL value rise, double-J ureteral stent placement should be considered. And this procedure is recommended to be finished in the most limited duration.

NGAL was purified from the secondary granules of human neutrophils for the first time in the early 1990s [4, 5]. Molecular biology study revealed that the NGAL molecule exists in three different molecular forms in blood and urine, a 25-kDa monomer, a 45-kDa disulphide-linked homodimer and a 135-kDa heterodimer, covalently conjugated with gelatinase [4, 5]. Cowland et al. [26] demonstrated that NGAL mRNA is expressed in several non-haematopoietic tissues, such as colon, trachea, lung and kidney epithelium and so on. NGAL level increases unpredictably during including AKI but also during other chronic and acute inflammatory conditions, such as in sepsis, during UTI, in CKDs, after CPB surgery and during acute exacerbations of obstructive pulmonary diseases [23, 27–29]. Therefore, patients with above-mentioned disease status were excluded in our research. The main research objects were patients with unilateral ureteral calculi and undergoing subclinical AKI. However, NGAL is also a useful marker in CKD and it has the potential to be an ideal biomarker in early detection of CKD, as well as a positive correlation with disease severity. In order to generalize the clinical application of NGAL, further researches involving the clinical significance of NGAL in patients with unilateral obstructive nephropathy could be considered [30]. In this study, the uNGAL level was 48.87 ± 30.18 ng/mL in the baseline. Urbschat et al. [21] reported that this value in healthy control subjects was 24.55 ± 40.12 ng/mL in their research. Though we did not detect the value in normal persons, patients diagnosed with ureteral calculi presenting renal colic showed a remarkable increase in the uNGAL values when sCr was within normal range compared to Urbschat's results, predicting that those patients might have likely subclinical AKI. Besides, we found both group 1 and group 2 patients did not show any diagnostic increases in sCr 2 h and 1 day after treatments. Nevertheless, uNGAL represented a significant change. These findings are consistent with the literatures and meaning uNGAL is an effective biomarker to monitor renal function. However, the cutoff NGAL concentration for optimal sensitivity and specificity to predict AKI is still ambiguous. As reported, it ranged from 100 to 270 ng/mL across all settings, with higher values for adults (170 ng/mL) compared with children (100–135 ng/mL). But there was large agreement on a cutoff value 150 ng/mL when NGAL was measured using standardized platforms, contrasting with large variability in cutoff values derived from research-based NGAL assays [1]. In this study, we also found if we use the cutoff value of 150 ng/mL, we could identify 1 more AKI case than sCr (+) alone. Unfortunately, the clinical application value is limited, mainly due to the limited sample size. And maybe a more reasonable cutoff value of uNGAL is expected.

Furthermore, some other investigators considered URS procedure would possibly affect renal function [22, 31], and was mainly because of the surgical tools, the high-pressure fluid used during the URS procedure and even the anaesthetics. The variation in NGAL can be identified within 2 h post-operation [11]. However, in our research, the uNGAL level decreased as time went by after placing the double-J ureteral stent. That is because ureteroscope was used under low-pressure mode, and ureteroscope only entered the bladder instead of entering the ureter during the procedure in this research. The mean operation time of total procedure was only 6.5 ± 4.2 min and only local infiltration anesthesia of urethral mucosa was performed instead of general anesthesia or lumbar anesthesia. Visibly, double-J ureteral stent placement is a protective factor of kidney injury for ureteral calculi patients with uNGAL rise.

However, our study has few limitations. Firstly, it was conducted in a single institution and may undergo selection bias. Secondly, it was a retrospective study with very limited sample size. Thirdly, it included only Chinese men. The population within each country differs culturally and sociodemographically. Fourthly, we did not consider economical pressure caused by double-J ureteral stent placement. As a result, further prospective, large-scale and well-designed studies should be conducted in multicenters. Also our Chinese-oriented results need to be validated in other ethnic groups and verified in unilateral obstructive nephropathy. Furthermore, there is still lack of valid assays to detect different types of NGAL forms [32–34]. Applying NGAL to the clinical evaluation of patients with or at risk of AKI has to wait until assays measuring kidney-specific NGAL are available and a reasonable cutoff value of uNGAL to distinguish normality and abnormity.

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Author contributions SQ: project development, data collection and management, data analysis, manuscript writing; YH: data collection and management, data analysis, manuscript editing, technical support; NW: data collection, data analysis; YD: data collection; JQ: project development, manuscript editing, technical support, supervision; YJY: project development, manuscript editing, technical support, supervision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Xinhua Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR (2011) The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 57(17):1752–1761. https://doi.org/10.1016/j.jacc.2010.11.051
2. Tsigou E, Psallida V, Demponeras C, Boutzouka E, Baltopoulos G (2013) Role of new biomarkers: functional and structural damage. Crit Care Res Pract 2013:361078. https://doi.org/10.1155/2013/361078
3. Devarajan P (2010) Review: neutrophil gelatinase-associated lipocalin: a troponin-like biomarker for human acute kidney injury. Nephrology (Carlton, Vic) 15(4):419–428. https://doi.org/10.1111/j.1440-1797.2010.01317.x
4. Kjeldsen L, Johnsen AH, Sengelov H, Borregaard N (1993) Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. J Biol Chem 268(14):10425–10432
5. Xu SY, Carlson M, Engstrom A, Garcia R, Peterson CG, Venge P (1994) Purification and characterization of a human neutrophil lipocalin (HNL) from the secondary granules of human neutrophils. Scand J Clin Lab Invest 54(5):365–376
6. Perrin T, Descombes E, Magnin JL, Gachet M, Hemett OM, Hayoz D, Stolt V, Baeriswyl G, Stauffer JC, Goy JJ, Togni M, Cook S (2013) Urinary neutrophil gelatinase-associated lipocalin (uNGAL) and contrast-induced acute kidney injury after coronary angiogram. Swiss Med Wkly 143:w13853. https://doi.org/10.4414/smw.2013.13853
7. Cruz DN, de Cal M, Garzotto F, Perazella MA, Lentini P, Corradi V, Piccinni P, Ronco C (2010) Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 36(3):444–451. https://doi.org/10.1007/s00134-009-1711-1
8. Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Dragun D, Haase M (2009) Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery—a prospective cohort study. Crit Care Med 37(2):553–560. https://doi.org/10.1097/CCM.0b013e318195846e
9. Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, Moretti E, Nguyen HB, Gunnerson K, Milzman D, Gaieski DF, Goyal M, Cairns CB, Kupfer K, Lee SW, Rivers EP (2010) The diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury in emergency department patients with suspected sepsis. Anna Emerg Med 56(1):52 e51–59 e51. https://doi.org/10.1016/j.annemergmed.2010.02.010
10. Hall IE, Yarlagadda SG, Coca SG, Wang Z, Doshi M, Devarajan P, Han WK, Marcus RJ, Parikh CR (2010) IL-18 and urinary NGAL predict dialysis and graft recovery after kidney transplantation. JASN 21(1):189–197. https://doi.org/10.1681/asn.2009030264

11. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P (2005) Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet (Lond, Engl) 365(9466):1231–1238. https://doi.org/10.1016/s0140-6736(05)74811-x
12. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P (2003) Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. JASN 14(10):2534–2543
13. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, Schmidt-Ott KM, Chen X, Li JY, Weiss S, Mishra J, Cheema FH, Markowitz G, Suganami T, Sawai K, Mukoyama M, Kunis C, D'Agati V, Devarajan P, Barasch J (2005) Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Investig 115(3):610–621. https://doi.org/10.1172/jci23056
14. Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, Devarajan P (2007) Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care (Lond Engl) 11(6):R127. https://doi.org/10.1186/cc6192
15. Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, Syed H, Ali S, Barasch J, Devarajan P (2008) Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. CJASN 3(3):665–673. https://doi.org/10.2215/cjn.04010907
16. Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, Lee HT (2006) Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology 105(3):485–491
17. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A (2009) Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 54(6):1012–1024. https://doi.org/10.1053/j.ajkd.2009.07.020
18. Haase M, Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Reade MC, Bagshaw SM, Seevanayagam N, Seevanayagam S, Doolan L, Buxton B, Dragun D (2009) Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. Crit Care Med 37(1):39–47. https://doi.org/10.1097/CCM.0b013e318193216f
19. Koyner JL, Vaidya VS, Bennett MR, Ma Q, Worcester E, Akhter SA, Raman J, Jeevanandam V, O'Connor MF, Devarajan P, Bonventre JV, Murray PT (2010) Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. CJASN 5(12):2154–2165. https://doi.org/10.2215/cjn.00740110
20. Matsui K, Kamijo-Ikemori A, Hara M, Sugaya T, Kodama T, Fujitani S, Taira Y, Yasuda T, Kimura K (2011) Clinical significance of tubular and podocyte biomarkers in acute kidney injury. Clin Exp Nephrol 15(2):220–225. https://doi.org/10.1007/s10157-010-0384-y
21. Urbschat A, Gauer S, Paulus P, Reissig M, Weipert C, Ramos-Lopez E, Hofmann R, Hadji P, Geiger H, Obermuller N (2014) Serum and urinary NGAL but not KIM-1 raises in human postrenal AKI. Eur J Clin Investig 44(7):652–659. https://doi.org/10.1111/eci.12283
22. Benli E, Ayyildiz SN, Cirrik S, Noyan T, Ayyildiz A, Cirakoglu A (2017) Early term effect of ureterorenoscopy (URS) on the kidney: research measuring NGAL, KIM-1, FABP and CYS C levels in urine. Int Braz J Urol 43(5):887–895. https://doi.org/10.1590/S1677-5538.IBJU.2016.0638
23. Martensson J, Bellomo R (2014) The rise and fall of NGAL in acute kidney injury. Blood Purif 37(4):304–310. https://doi.org/10.1159/000364937
24. Sivalingam S, Tamm-Daniels I, Nakada SY (2013) Office-based ureteral stent placement under local anesthesia for obstructing stones is safe and efficacious. Urology 81(3):498–502. https://doi.org/10.1016/j.urology.2012.10.021
25. Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, Janssen O, Philipp T, Kribben A (2004) Early detection of acute renal failure by serum cystatin C. Kidney Int 66(3):1115–1122. https://doi.org/10.1111/j.1523-1755.2004.00861.x
26. Cowland JB, Borregaard N (1997) Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. Genomics 45(1):17–23. https://doi.org/10.1006/geno.1997.4896
27. Xu S, Venge P (2000) Lipocalins as biochemical markers of disease. Biochem Biophys Acta 1482(1–2):298–307
28. Xu SY, Pauksen K, Venge P (1995) Serum measurements of human neutrophil lipocalin (HNL) discriminate between acute bacterial and viral infections. Scand J Clin Lab Investigation 55(2):125–131. https://doi.org/10.3109/00365519509089604
29. Fjaertoft G, Foucard T, Xu S, Venge P (2005) Human neutrophil lipocalin (HNL) as a diagnostic tool in children with acute infections: a study of the kinetics. Acta Paediatr (Oslo Nor 1992) 94(6):661–666. https://doi.org/10.1080/08035250510031610
30. Lalanne A, Beaudeux JL, Bernard MA (2011) NGAL: a biomarker of acute and chronic renal dysfunction. Ann Biol Clin 69(6):629–636. https://doi.org/10.1684/abc.2011.0646
31. Caddeo G, Williams ST, McIntyre CW, Selby NM (2013) Acute kidney injury in urology patients: incidence, causes and outcomes. Nephro-Urol Mon 5(5):955–961. https://doi.org/10.5812/numonthly.12721
32. Cai L, Rubin J, Han W, Venge P, Xu S (2010) The origin of multiple molecular forms in urine of HNL/NGAL. CJASN 5(12):2229–2235. https://doi.org/10.2215/cjn.00980110
33. Martensson J, Xu S, Bell M, Martling CR, Venge P (2012) Immunoassays distinguishing between HNL/NGAL released in urine from kidney epithelial cells and neutrophils. Clin Chimi Acta Int J Clini Chem 413(19–20):1661–1667. https://doi.org/10.1016/j.cca.2012.05.010
34. Glassford NJ, Schneider AG, Xu S, Eastwood GM, Young H, Peck L, Venge P, Bellomo R (2013) The nature and discriminatory value of urinary neutrophil gelatinase-associated lipocalin in critically ill patients at risk of acute kidney injury. Intensive Care Med 39(10):1714–1724. https://doi.org/10.1007/s00134-013-3040-7