

Novel biomarkers of acute kidney injury: Evaluation and evidence in urologic surgery

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Abstract

Patients undergoing urologic surgery are at risk of acute kidney injury (AKI) and consequently long-term deterioration in renal function. AKI is further associated with significantly higher odds of perioperative complications, prolonged hospital stay, higher mortality and costs. Therefore, better awareness and detection of AKI, as well as identification of AKI determinants in the urological surgery setting is warranted to pre-empt and mitigate further deterioration of renal function in patients at special risk. New consensus criteria provide precise definitions of diagnosis and description of the severity of AKI. However, they rely on serum creatinine (SCr), which is known to be an inaccurate marker of early changes in renal function. Therefore, several new urinary and serum biomarkers promise to address the gap associated with the use of SCr. Novel biomarkers may complement SCr measurement or most likely improve the diagnostic accuracy of AKI when used in combinations. However, novel biomarkers have to prove their clinical applicability, accuracy, and cost effectiveness prior to implementation into clinical practice. Most preferably, novel biomarkers should help to positively improve a patient's long-term renal functional outcomes. The purpose of this review is to discuss currently available biomarkers and to review their clinical evidence within urologic surgery settings.

Key words: Acute kidney injury; Urology; Outcome; Renal function; Biomarker; Surgery

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Core tip: Patients undergoing renal surgery represent a unique population at risk of acute kidney injury (AKI). AKI is known to be associated with adverse perioperative

outcomes. Therefore, efforts are warranted to promote awareness for AKI. Novel biomarkers promise to improve early and accurate detection of AKI, which may help to provide better patients' outcomes. However, these biomarkers still have to prove their clinical effectiveness prior to their implementation into urologic surgery settings.

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INTRODUCTION

Urologic patients are at risk of acute kidney injury (AKI)^[1-3]. A recent study evaluating procedure-dependent incidence of AKI in patients undergoing urologic surgery found that AKI was most frequently associated with partial/radical nephrectomy and nephroureterectomy (43.1%), transurethral resection of bladder tumor (15.3%), cystoprostatectomy (3.6%), ureteroscopy lithotripsy (3.6%), transurethral resection of the prostate (2.2%), radical prostatectomy (1.5%) and JJ-stent insertion (1.5%)^[4].

Potentially reversible causes of AKI related to urologic surgery may be of pre- (*e.g.*, postoperative bleeding, sepsis) or post-renal (*e.g.*, urinary obstruction, dislocation of ureteric stent, anastomotic leak) origin. However, AKI observed in renal surgery patients is largely related to direct renal damage, resulting in a potentially irreversible decline of renal function. Although partial nephrectomy for renal cell carcinoma aims to preserve renal function, AKI following the direct removal of renal parenchyma and damage of the remaining tissue from hyperfiltration or ischemia is a commonly observed adverse event in these patients^[5,6]. Besides the volume of preserved renal parenchyma, type and duration of ischemia during partial nephrectomy remain the most important modifiable factors for renal functional outcome^[7].

Ischemic renal injury leads to a robust inflammatory response within the kidney, but also extrarenal manifestations have been observed^[8-10]. Furthermore, the impact of renal ischemia-reperfusion injury on tumor propagation, malignant progression, and resistance to therapy is a topic of current investigations^[11,12]. In addition, there is evidence demonstrating an impact of postoperative AKI on adverse surgical outcomes^[13]. Indeed, AKI is associated with higher complication rates, longer hospital stays, increased mortality, and therefore greater utilization of health care resources and associated costs^[14,15]. As patients undergoing urologic oncologic surgery often present with (unknown) pre-existing chronic kidney disease (CKD) at the time of

surgery^[16,17] an additional perioperative episode of AKI may contribute to worse renal recovery, long-term renal function deterioration and progression of CKD^[3,18]. Consequently, urologists need to seek out the risk factors for AKI, identify the present signs and foresee its impact on the perioperative outcome of their patients^[13].

While there are excellent reviews highlighting the most promising urinary and serum biomarkers of AKI^[19,20], the purpose of this review is to discuss currently available biomarkers and to review their clinical evidence within urologic surgery settings.

DATA ACQUISITION

A non-systematic PubMed/Medline literature search was performed to identify original articles, review articles, and editorials evaluating AKI biomarkers in urologic surgery using the keywords "acute kidney injury, biomarkers, surgery, urology," of the last 3 years (May 30, 2001 to July 31, 2014). The literature search was restricted to English language and availability of full text.

RESULTS

Definition and diagnosis of acute kidney injury

Due to a lack of consensus on the definition of acute renal failure, a wide variation exists in estimates of disease prevalence and mortality^[15]. Currently, "AKI" is defined as an abrupt deterioration of kidney function and includes a spectrum ranging from minor renal functional impairment to acute renal failure requiring renal replacement therapy. The Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) staging criteria was the first consensus definition for AKI^[21], followed by the Acute Kidney Injury Network (AKIN) classification, which defines AKI as an absolute increase in the serum creatinine (SCr) concentration of ≥ 0.3 mg/dL from baseline within 48 h^[22]. More recently, the Kidney Disease/Improving Global Outcomes (KDIGO) group revised the definition of AKI, retaining AKIN staging criteria by classifying patients according to changes in SCr and urine output^[23]. RIFLE, AKIN and KDIGO definitions have emphasized on the non-negligible incidence of AKI and its long-term adverse outcomes^[21-23].

Biomarkers of acute kidney injury

Serum creatinine: SCr, is the gold-standard marker for renal function. However, SCr concentrations can be affected by age, gender, and racial differences of body mass as well as dietary factors and volume status^[24]. In general, equations that estimate renal function, such as the Modification of Diet in Renal Disease or the Chronic Kidney Disease Epidemiology Collaboration equations^[25,26], attempt to overcome the relative inaccuracy of SCr by including these patient characteristics to estimate glomerular filtration rate

Table 1 Baseline reference values of novel biomarkers of acute kidney injury obtained from different studies

Biomarker	Injury	Source	Test	Unit	Healthy controls (range)
Cystatin C	Proximal tubule injury	Serum	Nephelometric immunoassay/ELISA	mg/L	0.53-0.95 ^[38] 0.85 ± 0.21 ^[39]
		Urine	Nephelometric immunoassay/ELISA	mg/L	0.05 ¹ -0.28 ^[37] 0.02-0.11 ^[96]
NGAL	Ischemia and nephrotoxins	Serum	ELISA	ng/mL	86.3 ± 43.0 (men) ^[54] 88.9 ± 38.2 (women) ^[54] 56.71 ± 17.57 ^[39] 1.7 ± 0.5 ^[55] 0.4-10 ^[56]
		Urine	ELISA	ng/mL	5.7-17.7 ^[55] 11.94 ± 8.09 ^[39] 0.8-28.9 (men) ^[96] 1.9-316.7 (women) ^[96]
KIM-1	Ischemia and nephrotoxins	Urine	ELISA	pg/mL	59-2146 ^[70] 395.1 ± 398.8 ^[39] 31.0-1000.0 ^[56] 31.0-1736.5 ^[96]
IL-18	Toxic, delayed graft function	Urine	ELISA	pg/mL	1.4-1.8 ^[80] 3.0-108.6 ^[96] 6.2-311.1 ^[96]
L-FABP	Ischemia and nephrotoxins	Urine	ELISA	ng/mL	3-400 ^[83]
NAG	Tubule injury	Urine	Colorimetry	U/g	5.67 (2.74-8.21) ^[87] 0.75-0.90 U/g ^[95]
				U/g	1.06 ± 0.1 U/g (children) ^[90]

¹Lower reference values are not presented due to the detection limit of 0.05 mg/L. NGAL: Neutrophil gelatinase-associated lipocalin; KIM-1: Kidney injury molecule-1; IL-18: Interleukin-18; L-FABP: Liver-type fatty acid binding protein; NAG: N-acetyl-β-D-glucosaminidase; ELISA: Enzyme-linked immunosorbent assay; U: Unit.

(GFR)^[27]. Nonetheless SCr is primarily a marker of glomerular function, and SCr-based measurements may be inaccurate in detecting an abrupt decline in renal function, as the functional reserve of the remaining healthy nephrons prevents a significant rise in SCr until 50% of nephrons are lost^[28,29]. Furthermore, the early phase of AKI is accompanied with few symptoms or may even be asymptomatic. Thus, it is critical to note that even if the SCr-based estimation of renal function is "normal", loss of renal reserve may already have begun.

Consequently, recent research has focused on novel biomarkers that are directly related to the underlying renal injury and may diagnose AKI more expeditiously and accurately, while concurrently predicting its severity^[30,31]. Most perioperative studies on AKI have been performed in the setting of cardiac surgery. However, as the awareness of AKI is increasing, other surgical specialties are evaluating this adverse outcome as well^[32,33]. Additional biomarkers of AKI to rely on would be preferable especially in urologic high-risk patients (e.g., renal surgery, pre-existing CKD). In fact, several promising serum and urinary biomarkers are now available including serum and urinary Cystatin C (sCysC and uCysC), neutrophil gelatinase-associated lipocalin (sNGAL and uNGAL), and urinary Kidney Injury Molecule 1 (uKIM-1), Interleukin-18 (uIL-18), Liver-type fatty acid binding protein (uL-FABP) and N-acetyl-β-D-glucosaminidase (uNAG)^[34]. However, these biomarkers are still under investigation: baseline values are often

obtained from healthy volunteers and optimal cut-off values to define AKI need to be determined (Table 1). Some of these biomarkers already demonstrated additional prognostic value in the urologic surgery setting (Table 2), whereas others have yet to prove their clinical utility.

Novel biomarkers of acute kidney injury

Serum and urinary cystatin C: CysC is a low-molecular weight protein that is freely filtered across the glomerular membrane and in consequence less reliant on age, sex, race and muscle mass, compared to SCr^[35]. Moreover, although CysC is not normally detected in the urine, it has been found in the urine of patients with tubular disease, suggesting its putative role as a marker of renal tubular damage^[36]. Nephelometric measurements of CysC have upper reference values of 0.28 mg/L^[37] in the urine and range between 0.53-0.95 mg/L in the serum of healthy individuals^[38,39].

CysC has been proposed as a complementary or possibly marker of baseline renal function^[35,40]. Although sCysC measurement is currently 10 times more expensive than SCr, it is implemented in routine renal function measurement of pediatric patients and used to monitor kidney transplant patients^[41-43]. Furthermore, there is evidence suggesting that an elevation of sCysC predates minor decreases in GFR 1 to 2 d prior to symptoms, SCr elevation and/or renal function decline^[40,44,45]. Early elevations of uCysC levels were significant predictors of AKI after elective cardiac surgery^[46], and are correlated

Table 2 Biomarkers of acute kidney injury evaluated within urologic surgery settings

Ref.	Biomarker	Source	Cohort	Surgical setting	Outcome	Comparison	Time
Langetepe <i>et al</i> ^[65]	CysC, NGAL, KIM-1	Urine Serum	31 RCC patients	PN, RN	Increased values of CysC, NGAL, KIM-1 NGAL significant correlation to Cr No advantage for earlier detection of renal injury	Pre-/postoperative	24 h after surgery
Sprenkle <i>et al</i> ^[63]	NGAL	Urine	PN: 88 patients, RN: 32 patients, thoracic surgery: 42 patients	PN, RN (warm or cold ischemia)	No association between postoperative NGAL and any AKI AKI was not significantly associated with increased NGAL in PN patients No correlation with ischemia time Patients with eGFR < 60 mL/min per 1.73 m ² had higher NGAL postoperatively than those with an eGFR > 60 mL/min per 1.73 m ²	PN/RN /thoracic surgery patients	4, 8, 12, 24 h post surgery
Parekh <i>et al</i> ^[62]	Cr, NGAL, CysC, NGAL, LFABP, NAG, KIM-1, IL-18	Serum Urine, (renal mass biopsy)	20 patients with renal mass	PN (warm or cold ischemia)	Cr was significantly increased at 24 h CysC was not significantly changed at 2 or 24 h Significant increases serum NGAL at 2 and 24 h, increase of NGAL with increased ischemia time, no relation to peak Cr or morphology-score Early increases of L-FABP Early increase of NAG Increased NGAL at all times KIM-1 maximally increased at 24 h IL-18 was increased at all time points	Correlation to renal biopsies (pre-, intra. postoperative)	2 or 24 h after surgery
Schmid <i>et al</i> ^[50]	Cr, CysC	Serum	31 RCC patients	PN, RN	Postoperative Cysc and Cr elevations similarly predict renal function deterioration CysC-based GFR appears superior to eGFR in "Cr-blind" area	Pre-/postoperative, 1 yr follow up	24 h, 1 yr after surgery
Xue <i>et al</i> ^[76]	Cr, NGAL, KIM-1	Serum Urine	90 patients with obstructive uropathy	NA	KIM-1 and NGAL good accuracy for detecting AKI KIM-1 predicts the renal outcome 72 h postoperatively	Pre-/postoperative	4, 8, 12, 24, 48, 72 h after surgery
Cost <i>et al</i> ^[66]	NGAL	Urine (bladder and renal pelvis)	61 pediatric patients with ureteropelvic junction obstruction	Pyeloplasty	Significantly increased bladder NGAL Inverse correlation of bladder and renal pelvic NGAL levels with the differential renal function of the affected kidney	Healthy children	Intraoperative
Zekey <i>et al</i> ^[64]	Cr, NGAL	Serum Urine	40 patients with kidney stones	SWL	No statistical Cr and urine NGAL levels	Before/after intervention	day 1, 2, 7 after intervention
Fahmy <i>et al</i> ^[74]	KIM-1, NAG	Urine	60 patients with kidney stones (50 SWL, 10 URS)	SWL, URS	KIM-1 values were increased in patients with kidney stones when compared with volunteers KIM-1 and NAG levels significantly increased post-SWL Poor kidney function was significantly associated with increased KIM-1 and NAG baseline and post-SWL No significant change in urinary KIM-1 and NAG concentrations before and after URS	Volunteers without kidney stones	2-3 h after intervention
Ng <i>et al</i> ^[82]	IL-18, NAG	Urine	206 patients with renal stones	SWL	Increased IL-18 and NAG I slower shock wave delivery group	60 vs 120 shock waves/min	After intervention
Hatipoğlu <i>et al</i> ^[73]	KIM-1 (free radical production)	Urine	30 patients with kidney stones	SWL	Significant increase of KIM-1	Pre-/postoperative	2 h after intervention

PN: Partial nephrectomy; RN: Radical nephrectomy; NGAL: Neutrophil gelatinase-associated lipocalin; KIM-1: Kidney injury molecule-1; URS: Ureterorenoscopy; SWL: Shockwave lithotripsy; Cr: Creatinine; CysC: Cystatin C; LFABP: Liver fatty acid-binding protein; NAG: N-acetyl-b-D-glucosaminidase; eGFR: Estimated glomerular filtration rate; RCC: Renal cell carcinoma; NA: Not available.

with the need for renal replacement therapy in patients with acute tubular necrosis^[47]. However, other studies

were not able to corroborate these findings^[37] and suggest that sCysC is unreliable in the context of

postrenal obstruction^[48]. Yet, uCysC was shown to be independently associated with mortality in critically ill patients with AKI^[49].

In patients undergoing partial or radical nephrectomy, elevations of both SCr and sCysC on postoperative day one predicted renal function deterioration one year after surgery, while sCysC correlated better to renal function estimates compared to SCr in the "SCr-blind" area^[50].

Serum and urinary NGAL: Production of NGAL, a lipocalin protein involved in innate immunity by binding iron to limit bacterial growth^[51], is upregulated following renal injury, and consequently detectable in serum and urine hours prior to functional changes^[52,53]. sNGAL values in healthy individuals should be around 86.3 ng/mL in men and 88.9 ng/mL in women^[39,54-56], but may increase > 10-fold in serum and > 100-fold in urine following an acute injury^[57].

A meta-analysis of 19 observational studies including 2500 patients was performed to estimate the diagnostic and prognostic accuracy of NGAL for AKI detection and to establish the role of urinary and serum NGAL in the context of AKI^[58]. Xin *et al.*^[59] showed that for patients undergoing cardiac surgery, an increase of sNGAL was not temporally different to the rise of SCr within 48 h after AKI, however uNGAL (and IL-18) significantly increased to a peak of 400 ng/mL within 2-4 h of AKI.

Induction of unilateral renal ischemia in animal models results in physiological changes of the ischemic and contralateral kidney, with a corresponding increase of uNGAL and decrease of renal function^[60,61]. Parekh *et al.*^[62] studied the renal response to > 30 min of warm or cold clamp ischemia in patients undergoing partial nephrectomy and observed significant increases in sNGAL 2 and 24 h after surgery. While levels of all urinary biomarkers studied (NGAL, KIM-1, IL-18, NAG, L-FABP) increased 2 and/or 24 h after surgery, sCysC levels did not change significantly (SWL)^[62]. Conversely, Sprenkle *et al.*^[63] did not observe increased uNGAL in partial nephrectomy patients within 24 h after surgery. Accordingly, no statistically significant change of uNGAL levels was observed in 40 nephrolithiasis patients treated with shock-wave lithotripsy^[64]. Yet, our own data showed increased levels of uNGAL, KIM-1 and uCysC in 31 patients 24 h after partial or radical nephrectomy, but only uNGAL was correlated with SCr-based measurement of renal function^[65]. Increased levels of uNGAL have also been obtained from bladder urine in children with ureteropelvic junction obstruction undergoing unilateral pyeloplasty^[66]. Finally, uNGAL may serve as an early indicator for cisplatin nephrotoxicity^[67], which may be useful for patients with muscle-invasive bladder undergoing neoadjuvant chemotherapy prior to radical cystectomy.

Urinary KIM-1: KIM-1 is a transmembrane glycoprotein undetectable in healthy kidney tissue, but it represents the most upregulated protein in proximal tubular cells after ischemic or nephrotoxic injury^[68]. KIM-1 can be

immediately detected in the urine following injury^[69,70]. A strong correlation between immunohistochemical KIM-1 expression and tubular cell injury was shown in renal allograft biopsies of patients with active antibody-mediated transplant rejection^[71], suggesting that KIM-1 is a reliable marker for tubular epithelial injury prior to elevated blood biochemical indexes and morphological changes. In addition, children with AKI following cardiac surgery demonstrated elevated uKIM-1 levels 12 h after surgery^[72]. KIM-1 is measured in the urine by means of enzyme-linked immunosorbent assay, with normal values ranging between 59-2146 pg/mL in the healthy population^[70,73].

A significant increase of uKIM-1 levels 2-3 h after SWL treatment^[74,75] suggests direct ischemic damage and the release of free radicals. Both uKIM-1 and uNGAL demonstrated accuracy in detecting AKI among patients undergoing surgery for obstructive nephropathy; furthermore they might play a potential role in predicting postoperative renal recovery and long-term renal outcome^[76,77].

Urinary IL-18: IL-18 is a pro-inflammatory cytokine that is activated in proximal tubule cells and excreted in the urine following a kidney injury. Increased expression of *IL-18* genes has been demonstrated after renal ischemic injury^[78]. Animal models revealed that *IL-18* stimulates a positive feedback *via* IL-18 receptor during renal obstruction, which further stimulates IL-18 production and gene expression^[79].

Initially described in the pediatric cardiac surgery setting, IL-18 the urine increased 6 h in after surgery, whereas SCr did not reveal AKI until 48-72 h after surgery^[55]. Moreover, uIL-18 also increased significantly in adults and peaked at 600 pg/mL within 2-4 h after AKI^[59]. Another study demonstrated an increase from 1.4 pg/mL to a peak of 234 pg/mL (about 25-fold) 12 h after cardiopulmonary bypass surgery in patients presenting AKI^[55]. In patients with respiratory distress syndrome experiencing AKI, median uIL-18 was 104 pg/mL (range: 0 to 955 pg/mL), compared to 0 (range: 0 to 173 pg/mL) in control patients; IL-18 levels of > 100 pg/mL were associated with a 6.5-fold higher risk of AKI 24 h after hospitalization. Furthermore, higher level of uIL-18 (and serum IL-18) in ICU patients developing (dialysis-dependent) AKI was independently associated with mortality^[80,81].

Finally, patients undergoing SWL showed a significant increase of uIL-18 (and uNAG) when treated with slower shock waves^[82].

Urinary L-FABP: L-FABP is a 14-kDa protein expressed in proximal tubular epithelial cells. The urine of healthy individuals contains approximately 16 ng/mL L-FABP^[83]. The gene responsible for L-FABP is associated with hypoxic stress. L-FABP binds unsaturated fatty acids and lipid peroxidation products during tissue injury from hypoxia^[84]. Urinary excretion of L-FABP thus reflects stress within proximal tubular epithelial cells,

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and its correlation with renal function deterioration has been reported with AKI following contrast nephropathy and cardiac surgery^[83,85]. Although uL-FABP may be a promising biomarker for early detection of AKI, as demonstrated in an animal model of ischemia-reperfusion^[86], or for prediction of the need for dialysis and in-hospital mortality^[87], its value in urologic surgery warrants further investigation.

NAG: NAG, a tubular lysosomal brush border enzyme, is released into the urine following (reversible) renal proximal tubule injury. NAG is elevated in the urine of children with chronic renal obstruction^[88], regardless of the grade of hydronephrosis^[89], and following AKI^[90,91]. Rat models with isolated blunt renal trauma showed increased uNAG in the early stage after injury^[92]. However, the clinical utility of NAG remains limited as the urinary excretion of this enzyme is also increased in glomerular diseases such as diabetic nephropathy^[93]. The combination of urinary L-FABP (high sensitivity) and uNAG or uNGAL (high specificity) may enhance the detection of early postoperative AKI in patients undergoing cardiac surgery^[94,95].

CONCLUSION

A plethora of novel biomarkers for AKI have recently been described. Whereas sCysC, uCysC, sNGAL, uNGAL, uKIM-1 and uNAG have shown promise, we did not find convincing evidence for uIL-18 and uL-FABP. However, from a clinical perspective current use of these biomarkers in the urologic surgery setting is rare. Notable reasons behind this are the limited availability of assays, additional cost and the (currently) poor sensitivity and specificity demonstrated in urologic patients. Consequently, until now none of these biomarkers has been able to allow early detection of AKI in a way that would positively improve a patient's long-term outcomes and justify a regular implementation in specific urologic surgery settings. SCr remains the mainstay for evaluation of kidney function in urologic surgical patients. However, novel biomarkers may complement SCr measurement to indicate the need for urgent drainage or initiation of renoprotective measures. Moreover, it is likely that a combined use of these novel biomarkers will be needed to improve the diagnostic accuracy of AKI. Multiplex assays for simultaneous quantification of several biomarkers promise to overcome the flaws of single marker use and demonstrate the advantage of combinations reflecting different aspects of renal injury^[96]. While these assays are currently more expensive compared to traditional SCr measurement, the hope is that the incremental diagnostic accuracy would offset costs by mitigating costly associated complications of AKI.

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