**Name of journal: World Journal of Nephrology**

**ESPS Manuscript NO: 12592**

**Columns: Review**

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

Schmid M *et al*.Acute kidney injury in urologic surgery

Marianne Schmid, Deepansh Dalela, Rana Tahbaz, Jessica Langetepe, Marco Randazzo, Roland Dahlem, Margit Fisch, Quoc-Dien Trinh, Felix K.-H. Chun

**Marianne Schmid,Deepansh Dalela, Quoc-Dien Trinh**, Center for Surgery and Public Health and Division of Urologic Surgery, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115, United States

**Marianne Schmid, Rana Tahbaz,Jessica Langetepe, Roland Dahlem, Margit Fisch, Felix K.-H. Chun**, Department of Urology, University Hospital Hamburg-Eppendorf, 20246 Hamburg, Germany

**Deepansh Dalela**, Center for Outcomes Research, Analytics and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI 48202, United States

**Marco Randazzo**, Department of Urology, Cantonal Hospital Aarau, 5000 Aarau, Switzerland

**Author contributions:** All authors of this paper have substantially participated in the planning, execution, and data interpretation of the study; in addition, they have written, read and approved the final version submitted; all the authors contributed to the study concept, design, acquisition, interpretation, drafting, critically revision for important intellectual content of the manuscript.

**Conflict-of-interest:** The authors have no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Felix K.-H. Chun, MD**, **Associate Professor** of Urology, Department of Urology, University Hospital Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. chun@uke.de

**Telephone:** +49-40-741053486

**Received:** July 16, 2014

**Peer-review started:** July 17, 2014

**First decision:** August 14, 2014

**Revised:** December 30, 2014

**Accepted:** Janurary 15, 2015

**Article in press:**

**Published online:**

**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.

**Keywords:** Acute kidney injury; Renal function; Biomarker; Urology; Surgery; Outcome

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Schmid M, Dalela D, Tahbaz R, Langetepe J, Randazzo M, Dahlem R, Fisch M, Trinh QD, Chun F K.-H. Novel biomarkers of acute kidney injury: Evaluation and evidence in urologic surgery. *World J Nephrol* 2015; In press

**INTRODUCTION**

Urologic patients are at risk of acute kidney injury (AKI)[[1-3](#_ENREF_1)]. 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%), ureteroscopic lithotripsy (3.6%), transurethral resection of the prostate (2.2%), radical prostatectomy (1.5%) and JJ-stent insertion (1.5%)[[4](#_ENREF_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](#_ENREF_5),[6](#_ENREF_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](#_ENREF_7)].

Ischemic renal injury leads to a robust inflammatory response within the kidney, but also extrarenal manifestations have been observed[[8-10](#_ENREF_8)]. Furthermore, the impact of renal–ischemia reperfusion injury on tumor propagation, malignant progression, and resistance to therapy is a topic of current investigations[[11](#_ENREF_11),[12](#_ENREF_12)]. In addition, there is evidence demonstrating an impact of postoperative AKI on adverse surgical outcomes[[13](#_ENREF_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](#_ENREF_14),[15](#_ENREF_15)]. As patients undergoing urologic oncologic surgery often present with (unknown) pre-existing chronic kidney disease (CKD) at the time of surgery[[16](#_ENREF_16),[17](#_ENREF_17)] an additional perioperative episode of AKI may contribute to worse renal recovery, long-term renal function deterioration and progression of CKD[[3](#_ENREF_3),[18](#_ENREF_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](#_ENREF_13)].

While there are excellent reviews highlighting the most promising urinary and serum biomarkers of AKI[[19](#_ENREF_19),[20](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_23)]. RIFLE, AKIN and KDIGO definitions have emphasized on the non-negligible incidence of AKI and its long-term adverse outcomes[[21-23](#_ENREF_21)].

***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](#_ENREF_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](#_ENREF_25),[26](#_ENREF_26)], attempt to overcome the relative inaccuracy of SCr by including these patient characteristics to estimate glomerular filtration rate (GFR)[[27](#_ENREF_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](#_ENREF_28),[29](#_ENREF_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](#_ENREF_30),[31](#_ENREF_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](#_ENREF_32),[33](#_ENREF_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-ß-D-glucosaminidase (uNAG)[[34](#_ENREF_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](#_ENREF_35)]. Moreover, although CyC 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](#_ENREF_36)]. Nephelometric measurements of CysC have upper reference values of 0.28 mg/L[[37](#_ENREF_37)] in the urine and range between 0.53-0.95 mg/L in the serum of healthy individuals[[38](#_ENREF_38),[39](#_ENREF_39)].

CysC has been proposed as a complementary or possibly marker of baseline renal function[[35](#_ENREF_35),[40](#_ENREF_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](#_ENREF_41)]. 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](#_ENREF_40),[44](#_ENREF_44),[45](#_ENREF_45)]. Early elevations of uCysC levels were significant predictors of AKI after elective cardiac surgery[[46](#_ENREF_46)], and are correlated with the need for renal replacement therapy in patients with acute tubular necrosis[[47](#_ENREF_47)]. However, other studies were not able to corroborate these findings[[37](#_ENREF_37)] and suggest that sCysC is unreliable in the context of postrenal obstruction[[48](#_ENREF_48)]. Yet, uCysC was shown to be independently associated with mortality in critically ill patients with AKI[[49](#_ENREF_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](#_ENREF_50)].

**Serum and urinary Neutrophil gelatinase-associated lipocalin:** Production of NGAL, a lipocalin protein involved in innate immunity by binding iron to limit bacterial growth[[51](#_ENREF_51)], is upregulated following renal injury, and consequently detectable in serum and urine hours prior to functional changes[[52](#_ENREF_52),[53](#_ENREF_53)]. sNGAL values in healthy individuals should be around 86.3 ng/mL in men and 88.9 ng/mL in women[[39](#_ENREF_39),[54-56](#_ENREF_54)], but may increase > 10-fold in serum and > 100-fold in urine following an acute injury[[57](#_ENREF_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](#_ENREF_58)]. Xin *et al*[[59](#_ENREF_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](#_ENREF_60),[61](#_ENREF_61)]. Parekh *et al*[[62](#_ENREF_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[[62](#_ENREF_62)]. Conversely, Sprenkle *et al*[[63](#_ENREF_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](#_ENREF_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](#_ENREF_65)]. Increased levels of uNGAL have also been obtained from bladder urine in children with ureteropelvic junction obstruction undergoing unilateral pyeloplasty[[66](#_ENREF_66)]. Finally, uNGAL may serve as an early indicator for cisplatin nephrotoxicity[[67](#_ENREF_67)], which may be useful for patients with muscle-invasive bladder undergoing neoadjuvant chemotherapy prior to radical cystectomy.

**Urinary Kidney Injury Molecule 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](#_ENREF_68)]. KIM-1 can be immediately detected in the urine following injury[[69](#_ENREF_69),[70](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_70),[73](#_ENREF_73)].

A significant increase of uKIM-1 levels 2-3 h after SWL treatment[[74](#_ENREF_74),[75](#_ENREF_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](#_ENREF_76),[77](#_ENREF_77)].

**Urinary Interleukin-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](#_ENREF_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](#_ENREF_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](#_ENREF_55)]. Moreover, uIL-18 also increased significantly in adults and peaked at 600 pg/mL within 2-4 h after AKI[[59](#_ENREF_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](#_ENREF_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](#_ENREF_80),[81](#_ENREF_81)].

Finally, patients undergoing SWL showed a significant increase of uIL-18 (and uNAG) when treated with slower shock waves[[82](#_ENREF_82)].

**Urinary Liver-type fatty acid binding protein:** 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](#_ENREF_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](#_ENREF_84)]. Urinary excretion of L-FABP thus reflects stress within proximal tubular epithelial cells, and its correlation with renal function deterioration has been reported with AKI following contrast nephropathy and cardiac surgery[[83](#_ENREF_83),[85](#_ENREF_85)]. Although uL-FABP may be a promising biomarker for early detection of AKI, as demonstrated in an animal model of ischemia-reperfusion[[86](#_ENREF_86)], or for prediction of the need for dialysis and in-hospital mortality[[87](#_ENREF_87)], its value in urologic surgery warrants further investigation.

**N-acetyl-ß-D-glucosaminidase:** 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](#_ENREF_88)], regardless of the grade of hydronephrosis[[89](#_ENREF_89)] and following AKI[[90](#_ENREF_90),[91](#_ENREF_91)]. Rat models with isolated blunt renal trauma showed increased uNAG in the early stage after injury[[92](#_ENREF_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](#_ENREF_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](#_ENREF_94),[95](#_ENREF_95)].

**CONCLUSIONS**

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](#_ENREF_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.

**ACKNOWLEDGEMENTS**

Quoc-Dien Trinh is supported by the Professor Walter Morris-Hale Distinguished Chair in Urologic Oncology at the Brigham and Women’s Hospital

**REFERENCES**

1 **Wang SJ**, Mu XN, Zhang LY, Liu QY, Jin XB. The incidence and clinical features of acute kidney injury secondary to ureteral calculi. *Urol Res* 2012; **40**: 345-348 [PMID: 21853241 DOI: 10.1007/s00240-011-0414-6]

2 **Kim MJ**, Bachmann A, Mihatsch MJ, Ruszat R, Sulser T, Mayr M. Acute renal failure after continuous flow irrigation in patients treated with potassium-titanyl-phosphate laser vaporization of prostate. *Am J Kidney Dis* 2008; **51**: e19-e24 [PMID: 18371525 DOI: 10.1053/j.ajkd.2007.11.031]

3 **Cho A**, Lee JE, Kwon GY, Huh W, Lee HM, Kim YG, Kim DJ, Oh HY, Choi HY. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. *Nephrol Dial Transplant* 2011; **26**: 3496-3501 [PMID: 21406544 DOI: 10.1093/ndt/gfr094]

4 **Caddeo G**, Williams ST, McIntyre CW, Selby NM. Acute kidney injury in urology patients: incidence, causes and outcomes. *Nephrourol Mon* 2013; **5**: 955-961 [PMID: 24693501 DOI: 10.5812/numonthly.12721]

5 **Brenner BM**, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int* 1996; **49**: 1774-1777 [PMID: 8743495]

6 **Lane BR**, Babineau DC, Poggio ED, Weight CJ, Larson BT, Gill IS, Novick AC. Factors predicting renal functional outcome after partial nephrectomy. *J Urol* 2008; **180**: 2363-238; discussion 2363-238; [PMID: 18930264 DOI: 10.1016/j.juro.2008.08.036]

7 **Becker F**, Van Poppel H, Hakenberg OW, Stief C, Gill I, Guazzoni G, Montorsi F, Russo P, Stöckle M. Assessing the impact of ischaemia time during partial nephrectomy. *Eur Urol* 2009; **56**: 625-634 [PMID: 19656615 DOI: 10.1016/j.eururo.2009.07.016]

8 **Bonventre JV**, Zuk A. Ischemic acute renal failure: an inflammatory disease? *Kidney Int* 2004; **66**: 480-485 [PMID: 15253693 DOI: 10.1111/j.1523-1755.2004.761\_2.x]

9 **Hoke TS**, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, Tao Y, Dursun B, Voelkel NF, Edelstein CL, Faubel S. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. *J Am Soc Nephrol* 2007; **18**: 155-164 [PMID: 17167117 DOI: 10.1681/ASN.2006050494]

10 **Kramer AA**, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. *Kidney Int* 1999; **55**: 2362-2367 [PMID: 10354283 DOI: 10.1046/j.1523-1755.1999.00460.x]

11 **Höckel M**, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. *J Natl Cancer Inst* 2001; **93**: 266-276 [PMID: 11181773]

12 **Skolarikos AA**, Papatsoris AG, Alivizatos G, Deliveliotis C. Molecular pathogenetics of renal cancer. *Am J Nephrol* 2006; **26**: 218-231 [PMID: 16733347 DOI: 10.1159/000093631]

13 **Schmid M**, Abd-El-Barr AE, Gandaglia G, Sood A, Olugbade K, Ruhotina N, Sammon JD, Varda B, Chang SL, Kibel AS, Chun FK, Menon M, Fisch M, Trinh QD. Predictors of 30-day acute kidney injury following radical and partial nephrectomy for renal cell carcinoma. *Urol Oncol* 2014; **32**: 1259-1266 [PMID: 25129142 DOI: 10.1016/j.urolonc.2014.05.002]

14 **Chertow GM**, Soroko SH, Paganini EP, Cho KC, Himmelfarb J, Ikizler TA, Mehta RL. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. *Kidney Int* 2006; **70**: 1120-1126 [PMID: 16850028 DOI: 10.1038/sj.ki.5001579]

15 **Lameire NH**, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, Liu KD, Mehta RL, Pannu N, Van Biesen W, Vanholder R. Acute kidney injury: an increasing global concern. *Lancet* 2013; **382**: 170-179 [PMID: 23727171 DOI: 10.1016/S0140-6736(13)60647-9]

16 **Lane BR**, Poggio ED, Herts BR, Novick AC, Campbell SC. Renal function assessment in the era of chronic kidney disease: renewed emphasis on renal function centered patient care. *J Urol* 2009; **182**: 435-443; discussion 443-444 [PMID: 19524967 DOI: 10.1016/j.juro.2009.04.004]

17 **Schmid M**, Ravi P, Abd-El-Barr AE, Klap J, Sammon JD, Chang SL, Menon M, Kibel AS, Fisch M, Trinh QD. Chronic kidney disease and perioperative outcomes in urological oncological surgery. *Int J Urol* 2014; **21**: 1245-1252 [PMID: 25041641 DOI: 10.1111/iju.12563]

18 **Ali T**, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod A. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007; **18**: 1292-1298 [PMID: 17314324 DOI: 10.1681/ASN.2006070756]

19 **Lane BR**. Molecular markers of kidney injury. *Urol Oncol* 2013; **31**: 682-685 [PMID: 21723753 DOI: 10.1016/j.urolonc.2011.05.007]

20 **Slocum JL**, Heung M, Pennathur S. Marking renal injury: can we move beyond serum creatinine? *Transl Res* 2012; **159**: 277-289 [PMID: 22424431 DOI: 10.1016/j.trsl.2012.01.014]

21 **Bellomo R**, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**: R204-R212 [PMID: 15312219 DOI: 10.1186/cc2872

22 **Mehta RL**, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31 [PMID: 17331245 DOI: 10.1186/cc5713]

23 **KDIGO AKI Working Group**. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**: 1-138

24 **Michels WM**, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol* 2010; **5**: 1003-1009 [PMID: 20299365 DOI: 10.2215/CJN.06870909]

25 **Levey AS**, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**: 766-772 [PMID: 17332152 DOI: 10.1373/clinchem.2006.077180]

26 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: 19414839 DOI: 10.7326/0003-4819-150-9-200905050-00006]

27 **Levey AS**, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461-470 [PMID: 10075613 DOI: 10.7326/0003-4819-130-6-199903160-00002]

28 **Hayslett JP**. Functional adaptation to reduction in renal mass. *Physiol Rev* 1979; **59**: 137-164 [PMID: 220646]

29 **Hostetter TH**, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *J Am Soc Nephrol* 2001; **12**: 1315-1325 [PMID: 11373357]

30 **Coca SG**, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int* 2008; **73**: 1008-1016 [PMID: 18094679 DOI: 10.1038/sj.ki.5002729]

31 **Waikar SS**, Bonventre JV. Biomarkers for the diagnosis of acute kidney injury. *Nephron Clin Pract* 2008; **109**: c192-c197 [PMID: 18802367 DOI: 10.1159/000142928]

32 **Dedeoglu B**, de Geus HR, Fortrie G, Betjes MG. Novel biomarkers for the prediction of acute kidney injury in patients undergoing liver transplantation. *Biomark Med* 2013; **7**: 947-957 [PMID: 24266830 DOI: 10.2217/bmm.13.91]

33 **Sung WC**, Yu HP, Tsai YF, Chung PC, Lin CC, Lee WC. The ratio of plasma interleukin-18 is a sensitive biomarker for acute kidney injury after liver transplantation. *Transplant Proc* 2014; **46**: 816-817 [PMID: 24767355 DOI: 10.1016/j.transproceed.2013.09.055]

34 **Thomas AA**, Demirjian S, Lane BR, Simmons MN, Goldfarb DA, Subramanian VS, Campbell SC. Acute kidney injury: novel biomarkers and potential utility for patient care in urology. *Urology* 2011; **77**: 5-11 [PMID: 20599252 DOI: 10.1016/j.urology.2010.05.004]

35 **Roos JF**, Doust J, Tett SE, Kirkpatrick CM. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children--a meta-analysis. *Clin Biochem* 2007; **40**: 383-391 [PMID: 17316593 DOI: 10.1016/j.clinbiochem.2006.10.026]

36 **Conti M**, Moutereau S, Zater M, Lallali K, Durrbach A, Manivet P, Eschwège P, Loric S. Urinary cystatin C as a specific marker of tubular dysfunction. *Clin Chem Lab Med* 2006; **44**: 288-291 [PMID: 16519600 DOI: 10.1515/CCLM.2006.050]

37 **Royakkers AA**, van Suijlen JD, Hofstra LS, Kuiper MA, Bouman CS, Spronk PE, Schultz MJ. Serum cystatin C-A useful endogenous marker of renal function in intensive care unit patients at risk for or with acute renal failure? *Curr Med Chem* 2007; **14**: 2314-2317 [PMID: 17896979]

38 **Croda-Todd MT**, Soto-Montano XJ, Hernández-Cancino PA, Juárez-Aguilar E. Adult cystatin C reference intervals determined by nephelometric immunoassay. *Clin Biochem* 2007; **40**: 1084-1087 [PMID: 17624320 DOI: 10.1016/j.clinbiochem.2007.05.011]

39 **Matys U**, Bachorzewska-Gajewska H, Malyszko J, Dobrzycki S. Assessment of kidney function in diabetic patients. Is there a role for new biomarkers NGAL, cystatin C and KIM-1? *Adv Med Sci* 2013; **58**: 353-361 [PMID: 24384771 DOI: 10.2478/v10039-012-0077-8]

40 **Dharnidharka VR**, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002; **40**: 221-226 [PMID: 12148093 DOI: 10.1053/ajkd.2002.34487]

41 **Le Bricon T**, Thervet E, Benlakehal M, Bousquet B, Legendre C, Erlich D. Changes in plasma cystatin C after renal transplantation and acute rejection in adults. *Clin Chem* 1999; **45**: 2243-2249 [PMID: 10585359]

42 **Ayub S**, Zafar MN, Aziz T, Iqbal T, Khan S, Rizvi SA. Evaluation of renal function by cystatin C in renal transplant recipients. *Exp Clin Transplant* 2014; **12**: 37-40 [PMID: 24471722 DOI: 10.6002/ect.2013.0202]

43 **Fox JA**, Dudley AG, Bates C, Cannon GM. Cystatin C as a marker of early renal insufficiency in children with congenital neuropathic bladder. *J Urol* 2014; **191**: 1602-1607 [PMID: 24679869 DOI: 10.1016/j.juro.2013.09.093]

44 **Herget-Rosenthal S**, Marggraf G, Hüsing J, Göring F, Pietruck F, Janssen O, Philipp T, Kribben A. Early detection of acute renal failure by serum cystatin C. *Kidney Int* 2004; **66**: 1115-1122 [PMID: 15327406 DOI: 10.1111/j.1523-1755.2004.00861.x]

45 **Pirgakis KM**, Makris K, Dalainas I, Lazaris AM, Maltezos CK, Liapis CD. Urinary cystatin C as an early biomarker of acute kidney injury after open and endovascular abdominal aortic aneurysm repair. *Ann Vasc Surg* 2014; **28**: 1649-1658 [PMID: 24858592 DOI: 10.1016/j.avsg.2014.04.006]

46 **Koyner JL**, Bennett MR, Worcester EM, Ma Q, Raman J, Jeevanandam V, Kasza KE, O'Connor MF, Konczal DJ, Trevino S, Devarajan P, Murray PT. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. *Kidney Int* 2008; **74**: 1059-1069 [PMID: 18650797 DOI: 10.1038/ki.2008.341]

47 **Herget-Rosenthal S**, Poppen D, Hüsing J, Marggraf G, Pietruck F, Jakob HG, Philipp T, Kribben A. Prognostic value of tubular proteinuria and enzymuria in nonoliguric acute tubular necrosis. *Clin Chem* 2004; **50**: 552-558 [PMID: 14709451 DOI: 10.1373/clinchem.2003.027763]

48 **Hasslacher J**, Lehner GF, Joannidis M. Insufficient performance of serum cystatin C as a biomarker for acute kidney injury of postrenal etiology. *Intensive Care Med* 2012; **38**: 170-171 [PMID: 21965103 DOI: 10.1007/s00134-011-2384-0]

49 **Nejat M**, Pickering JW, Walker RJ, Westhuyzen J, Shaw GM, Frampton CM, Endre ZH. Urinary cystatin C is diagnostic of acute kidney injury and sepsis, and predicts mortality in the intensive care unit. *Crit Care* 2010; **14**: R85 [PMID: 20459852 DOI: 10.1186/cc9014]

50 **Schmid M**, Schwaiger B, Tenschert W, Shaffu M, Thabaz R, Langetepe J, Ahyai S, Eichelberg C, Fisch M, Chun F. Surveillance of renal function after (partial) tumor nephrectomy by Cystatin C-measurement. *Journal of Urology* 2013; **189**: Supplement e1-e952

51 **Yang J**, Goetz D, Li JY, Wang W, Mori K, Setlik D, Du T, Erdjument-Bromage H, Tempst P, Strong R, Barasch J. An iron delivery pathway mediated by a lipocalin. *Mol Cell* 2002; **10**: 1045-1056 [PMID: 12453413 DOI: 10.1016/S1097-2765(02)00710-4]

52 **Mishra J**, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am Soc Nephrol* 2003; **14**: 2534-2543 [PMID: 14514731 DOI: 10.1097/01.ASN.0000088027.54400.C6]

53 **Borregaard N**, Cowland JB. Neutrophil gelatinase-associated lipocalin, a siderophore-binding eukaryotic protein. *Biometals* 2006; **19**: 211-215 [PMID: 16718606 DOI: 10.1007/s10534-005-3251-7]

54 **Stejskal D**, Karpísek M, Humenanska V, Hanulova Z, Stejskal P, Kusnierova P, Petzel M. Lipocalin-2: development, analytical characterization, and clinical testing of a new ELISA. *Horm Metab Res* 2008; **40**: 381-385 [PMID: 18393169 DOI: 10.1055/s-2008-1062746]

55 **Parikh CR**, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, Dent C, Devarajan P, Edelstein CL. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2006; **70**: 199-203 [PMID: 16710348 DOI: 10.1038/sj.ki.5001527]

56 TECOmedical Group, Switzerland. Novel kidney injury biomarkers. Available from: URL: http: //www.tecomedical.com

57 **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. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 2005; **115**: 610-621 [PMID: 15711640 DOI: 10.1172/JCI23056]

58 **Haase M**, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. 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* 2009; **54**: 1012-1024 [PMID: 19850388 DOI: 10.1053/j.ajkd.2009.07.020]

59 **Xin C**, Yulong X, Yu C, Changchun C, Feng Z, Xinwei M. Urine neutrophil gelatinase-associated lipocalin and interleukin-18 predict acute kidney injury after cardiac surgery. *Ren Fail* 2008; **30**: 904-913 [PMID: 18925531 DOI: 10.1080/08860220802359089]

60 **Silberstein JL**, Sprenkle PC, Su D, Power NE, Tarin TV, Ezell P, Sjoberg DD, Feifer A, Fleisher M, Russo P, Touijer KA. Neutrophil gelatinase-associated lipocalin (NGAL) levels in response to unilateral renal ischaemia in a novel pilot two-kidney porcine model. *BJU Int* 2013; **112**: 517-525 [PMID: 23510358 DOI: 10.1111/bju.12066]

61 **Woodson BW**, Wang L, Mandava S, Lee BR. Urinary cystatin C and NGAL as early biomarkers for assessment of renal ischemia-reperfusion injury: a serum marker to replace creatinine? *J Endourol* 2013; **27**: 1510-1515 [PMID: 24266750 DOI: 10.1089/end.2013.0198]

62 **Parekh DJ**, Weinberg JM, Ercole B, Torkko KC, Hilton W, Bennett M, Devarajan P, Venkatachalam MA. Tolerance of the human kidney to isolated controlled ischemia. *J Am Soc Nephrol* 2013; **24**: 506-517 [PMID: 23411786 DOI: 10.1681/ASN.2012080786]

63 **Sprenkle PC**, Wren J, Maschino AC, Feifer A, Power N, Ghoneim T, Sternberg I, Fleisher M, Russo P. Urine neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after kidney surgery. *J Urol* 2013; **190**: 159-164 [PMID: 23391468 DOI: 10.1016/j.juro.2013.01.101]

64 **Zekey F**, Senkul T, Ates F, Soydan H, Yilmaz O, Baykal K. Evaluation of the impact of shock wave lithotripsy on kidneys using a new marker: how do neutrophil gelatinese-associated lypocalin values change after shock wave lithotripsy? *Urology* 2012; **80**: 267-272 [PMID: 22503759 DOI: 10.1016/j.urology.2012.02.015]

65 **Langetepe J**, Schmid M, Schwaiger B, Tahbaz R, Ahyai S, Eichelberg C, Fisch M, Chun F. Serum and urine biomarker profile of kidney injury after (partial) tumor nephrectomy. 2014. Available from: URL: http: //www.uroweb.org/events/abstracts-online/?AID=51341

66 **Cost NG**, Noh PH, Devarajan P, Ivancic V, Reddy PP, Minevich E, Bennett M, Haffner C, Schulte M, DeFoor WR. Urinary NGAL levels correlate with differential renal function in patients with ureteropelvic junction obstruction undergoing pyeloplasty. *J Urol* 2013; **190**: 1462-1467 [PMID: 23791906 DOI: 10.1016/j.juro.2013.05.003]

67 **Mishra J**, Mori K, Ma Q, Kelly C, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. *Am J Nephrol* 2004; **24**: 307-315 [PMID: 15148457 DOI: 10.1159/000078452]

68 **Bonventre JV**. Kidney injury molecule-1: a translational journey. *Trans Am Clin Climatol Assoc* 2014; **125**: 293-29; discussion 299 [PMID: 25125746]

69 **Devarajan P**. Biomarkers for the early detection of acute kidney injury. *Curr Opin Pediatr* 2011; **23**: 194-200 [PMID: 21252674 DOI: 10.1097/MOP.0b013e328343f4dd]

70 **Vaidya VS**, Ramirez V, Ichimura T, Bobadilla NA, Bonventre JV. Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. *Am J Physiol Renal Physiol* 2006; **290**: F517-F529 [PMID: 16174863 DOI: 10.1152/ajprenal.00291.2005]

71 **Song L**, Xue L, Yu J, Zhao J, Zhang W, Fu Y. Kidney injury molecule-1 expression is closely associated with renal allograft damage. *Bosn J Basic Med Sci* 2013; **13**: 170-174 [PMID: 23988168]

72 **Han WK**, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, Bonventre JV. Urinary biomarkers in the early diagnosis of acute kidney injury. *Kidney Int* 2008; **73**: 863-869 [PMID: 18059454 DOI: 10.1038/sj.ki.5002715]

73 **Chaturvedi S**, Farmer T, Kapke GF. Assay validation for KIM-1: human urinary renal dysfunction biomarker. *Int J Biol Sci* 2009; **5**: 128-134 [PMID: 19173034]

74 **Fahmy N**, Sener A, Sabbisetti V, Nott L, Lang RM, Welk BK, Méndez-Probst CE, MacPhee RA, VanEerdewijk S, Cadieux PA, Bonventre JV, Razvi H. Urinary expression of novel tissue markers of kidney injury after ureteroscopy, shockwave lithotripsy, and in normal healthy controls. *J Endourol* 2013; **27**: 1455-1462 [PMID: 24180435 DOI: 10.1089/end.2013.0188]

75 **Hatipoğlu NK**, Evliyaoğlu O, Işık B, Bodakçi MN, Bozkurt Y, Sancaktutar AA, Söylemez H, Atar M, Penbegül N, Yünce M, Dağgulli M. Antioxidant signal and kidney injury molecule-1 levels in shockwave lithotripsy induced kidney injury. *J Endourol* 2014; **28**: 224-228 [PMID: 24044353 DOI: 10.1089/end.2013.0535]

76 **Xue W**, Xie Y, Wang Q, Xu W, Mou S, Ni Z. Diagnostic performance of urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin for acute kidney injury in an obstructive nephropathy patient. *Nephrology* (Carlton) 2014; **19**: 186-194 [PMID: 24165570 DOI: 10.1111/nep.12173]

77 **Lucarelli G**, Mancini V, Galleggiante V, Rutigliano M, Vavallo A, Battaglia M, Ditonno P. Emerging urinary markers of renal injury in obstructive nephropathy. *Biomed Res Int* 2014; **2014**: 303298 [PMID: 25101270 DOI: 10.1155/2014/303298]

78 **Supavekin S**, Zhang W, Kucherlapati R, Kaskel FJ, Moore LC, Devarajan P. Differential gene expression following early renal ischemia/reperfusion. *Kidney Int* 2003; **63**: 1714-1724 [PMID: 12675847 DOI: 10.1046/j.1523-1755.2003.00928.x]

79 **VanderBrink BA**, Asanuma H, Hile K, Zhang H, Rink RC, Meldrum KK. Interleukin-18 stimulates a positive feedback loop during renal obstruction via interleukin-18 receptor. *J Urol* 2011; **186**: 1502-1508 [PMID: 21855933 DOI: 10.1016/j.juro.2011.05.046]

80 **Parikh CR**, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol* 2005; **16**: 3046-3052 [PMID: 16148039 DOI: 10.1681/ASN.2005030236]

81 **Lin CY**, Chang CH, Fan PC, Tian YC, Chang MY, Jenq CC, Hung CC, Fang JT, Yang CW, Chen YC. Serum interleukin-18 at commencement of renal replacement therapy predicts short-term prognosis in critically ill patients with acute kidney injury. *PLoS One* 2013; **8**: e66028 [PMID: 23741523 DOI: 10.1371/journal.pone.0066028]

82 **Ng CF**, Lo AK, Lee KW, Wong KT, Chung WY, Gohel D. A prospective, randomized study of the clinical effects of shock wave delivery for unilateral kidney stones: 60 versus 120 shocks per minute. *J Urol* 2012; **188**: 837-842 [PMID: 22819406 DOI: 10.1016/j.juro.2012.05.009]

83 **Matsui K**, Kamijo-Ikemori A, Sugaya T, Yasuda T, Kimura K. Usefulness of urinary biomarkers in early detection of acute kidney injury after cardiac surgery in adults. *Circ J* 2012; **76**: 213-220 [PMID: 22094907]

84 **Bennaars-Eiden A**, Higgins L, Hertzel AV, Kapphahn RJ, Ferrington DA, Bernlohr DA. Covalent modification of epithelial fatty acid-binding protein by 4-hydroxynonenal in vitro and in vivo. Evidence for a role in antioxidant biology. *J Biol Chem* 2002; **277**: 50693-50702 [PMID: 12386159 DOI: 10.1074/jbc.M209493200]

85 **Manabe K**, Kamihata H, Motohiro M, Senoo T, Yoshida S, Iwasaka T. Urinary liver-type fatty acid-binding protein level as a predictive biomarker of contrast-induced acute kidney injury. *Eur J Clin Invest* 2012; **42**: 557-563 [PMID: 22070248 DOI: 10.1111/j.1365-2362.2011.02620.x]

86 **Yamamoto T**, Noiri E, Ono Y, Doi K, Negishi K, Kamijo A, Kimura K, Fujita T, Kinukawa T, Taniguchi H, Nakamura K, Goto M, Shinozaki N, Ohshima S, Sugaya T. Renal L-type fatty acid--binding protein in acute ischemic injury. *J Am Soc Nephrol* 2007; **18**: 2894-2902 [PMID: 17942962 DOI: 10.1681/ASN.2007010097]

87 **Susantitaphong P**, Siribamrungwong M, Doi K, Noiri E, Terrin N, Jaber BL. Performance of urinary liver-type fatty acid-binding protein in acute kidney injury: a meta-analysis. *Am J Kidney Dis* 2013; **61**: 430-439 [PMID: 23228945 DOI: 10.1053/j.ajkd.2012.10.016]

88 **Carr MC**, Peters CA, Retik AB, Mandell J. Urinary levels of the renal tubular enzyme N-acetyl-beta-D-glucosaminidase in unilateral obstructive uropathy. *J Urol* 1994; **151**: 442-445 [PMID: 8283554]

89 **Skalova S**, Rejtar P, Kutilek S. Increased urinary N-acetyl-beta-D-glucosaminidase activity in children with hydronephrosis. *Int Braz J Urol* 2007; **33**: 80-83; discussion 84-86 [PMID: 17335604 DOI: 10.1590/S1677-55382007000100014]

90 **Bernard AM**, Vyskocil AA, Mahieu P, Lauwerys RR. Assessment of urinary retinol-binding protein as an index of proximal tubular injury. *Clin Chem* 1987; **33**: 775-779 [PMID: 3297418]

91 **Liangos O**, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, MacKinnon RW, Li L, Balakrishnan VS, Pereira BJ, Bonventre JV, Jaber BL. Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. *J Am Soc Nephrol* 2007; **18**: 904-912 [PMID: 17267747 DOI: 10.1681/ASN.2006030221]

92 **Hanbeyoğlu A**, Kazez A, Ustündağ B, Akpolat N. Determination of urinary N-acetyl-ß-D glucosaminidase (NAG) levels in experimental blunt renal trauma. *Ulus Travma Acil Cerrahi Derg* 2011; **17**: 475-481 [PMID: 22289997 DOI: 10.5505/tjtes.2011.57973]

93 **Marchewka Z**, Kuźniar J, Długosz A. Enzymuria and beta2-mikroglobulinuria in the assessment of the influence of proteinuria on the progression of glomerulopathies. *Int Urol Nephrol* 2001; **33**: 673-676 [PMID: 12452627]

94 **Katagiri D**, Doi K, Honda K, Negishi K, Fujita T, Hisagi M, Ono M, Matsubara T, Yahagi N, Iwagami M, Ohtake T, Kobayashi S, Sugaya T, Noiri E. Combination of two urinary biomarkers predicts acute kidney injury after adult cardiac surgery. *Ann Thorac Surg* 2012; **93**: 577-583 [PMID: 22269724 DOI: 10.1016/j.athoracsur.2011.10.048]

95 **Liu S**, Che M, Xue S, Xie B, Zhu M, Lu R, Zhang W, Qian J, Yan Y. Urinary L-FABP and its combination with urinary NGAL in early diagnosis of acute kidney injury after cardiac surgery in adult patients. *Biomarkers* 2013; **18**: 95-101 [PMID: 23167703 DOI: 10.3109/1354750X.2012.740687]

96 **Zhang X**, Gibson B, Mori R, Snow-Lisy D, Yamaguchi Y, Campbell SC, Simmons MN, Daly TM. Analytical and biological validation of a multiplex immunoassay for acute kidney injury biomarkers. *Clin Chim Acta* 2013; **415**: 88-93 [PMID: 23041213 DOI: 10.1016/j.cca.2012.09.022]

**P- Reviewer:** Carvalho M, Papatsoris AG, Simmons MN

**S- Editor:** Gong XM

**L- Editor:** **E- Editor:**

**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 | 0.051-0.28[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]  0.4-100[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[97]  6.2-311.1[97] |
| L-FABP | Ischemia and nephrotoxins | Urine | ELISA | ng/mL  μg/gCr | 3-400[83]  5.67 (2.74–8.21)[87] |
| NAG | Tubule injury | Urine | Colorimetry | U/g | 0.75–0.90 U/g[95]  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-ß-D-glucosaminidase; ELISA: Enzyme-linked immunosorbent assay; U: Unit.

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Biomarker** | **Source** | **Cohort** | **Surgical setting** | **Outcome** | **Comparison** | **Time** |
| Langetepe *et al*[65] | CysC, NGAL, KIM-1  Cr | Urine  Serum | 31 RCC patients | PN, RN | Increased values 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 *et al*[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 m2 had higher NGAL postoperatively than those with an eGFR > 60 ml/min per 1.73 m2 | PN/RN /thoracic surgery patients | 4, 8, 12, 24 h post surgery |
| Parekh *et al*[62] | Cr, NGAL, CysC  NGAL, LFABP, NAG,  KIM-1,  IL-18 | Serum  Urine,  (renal 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-1maximally 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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[82] | IL-18, NAG | Urine | 206 patinets with renal stones | SWL | Increased IL-18 and NAG I slower shock wave delivery group | 60 *vs* 120 shock waves/min | After intervention |
| Hatipoğlu *et al*[75] | 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: Kideny Injury Molecule 1; URS: Ureteroenocsopy; SWL: Shockwave lithotripsy; Cr: Creatinine; CysC: Cystatin C; LFABP: Liver fatty acid–binding protein; NAG: Nacetyl-b-D-glucosaminidase; eGFR: Estimated Glomerular filtration rate; RCC: Renal cell carcinoma; u: Urinary; NA: Not available.