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Review

Biomarkers for acute kidney injury

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Abstract

Objectives: Acute kidney injury (AKI) is associated with both a number of adverse outcomes and with morbidity and mortality. Therefore, early diagnosis of AKI is very important. Several novel AKI biomarkers have been found and studied. Markers include impaired filtration barriers, reduced tubular reabsorption, increased release of tubular proteins due to cell damage and/or activation of inflammatory cells, and the release of activation products in response to injury. Neutrophil gelatinase–associated lipocalin, kidney injury molecule 1, interleukin-18, liver-type fatty acid-binding protein, cystatin C, tissue inhibitor of metalloproteinase-2, and insulin-like growth factor-binding protein 7 markers appear to be useful; however, the clinical uses of AKI biomarkers are not yet well defined and the number of clinical trials is limited. Additionally, analytical validation of tests for AKI markers is also required. Therefore, measurement of the daily quantity of urine and determination of blood urea and creatinine levels are most often used for both diagnosis and classification of AKI in clinical practice.

Keywords: Acute kidney injury, cystatin c, insulin-like growth factor-binding protein 7, interleukin-18, kidney injury molecule 1, liver-type fatty acid–binding protein, neutrophil gelatinase-associated lipocalin, tissue inhibitor of metalloproteinase-2

Acute kidney injury (AKI) is the sudden loss of kidney function. It has been referred to as acute kidney failure in the past. The primary physiological function of the kidneys is to filter the blood and remove the waste, as well as excess salt and water. When AKI occurs, urea nitrogen and creatinine levels increase in the blood circulation, the daily urine output falls, and the fluid-electrolyte balance and the acid-base balance deteriorate. AKI is associated with prerenal, renal, and postrenal events (Table 1). Although AKI is often reversible, depending on the causes and severity, it may not be. The most common adverse events due to AKI are chronic renal failure, chronic kidney disease, and cardiovascular events. AKI is a major cause of morbidity and mortality in intensive care units. Therefore, early diagnosis of AKI is very important for the prognosis of patients as well as to reduce medical costs [1-6].

To diagnose AKI, the measurement of the daily quantity of urine output; routine urinalysis; blood tests examining urea and creatinine levels; imaging tests, such as ultrasound and computerized tomography; and/or a kidney biopsy may be performed. Regulation of blood pressure and circulation of the blood to the kidneys are primary treatments for patients with AKI. Short-term dialysis is used in some cases, but long-term dialysis or kidney transplantation may be required for patients with severe renal insufficiency [7, 8].

Several classification schemes have been proposed for patients with AKI according to the extent and duration of renal injury and to predict clinical outcomes (Table 2). The classification systems contain criteria for serum creatinine (SCr) and urine output. The KDIGO (Kidney Disease: Improving Global Outcomes) criteria for AKI diagnosis are: SCr level increase more than 0.3 mg/dL in 48 hours, or SCr level increase 1.5-fold over baseline within 7 days, or urine volume of less than 0.5 mL/kg/hour for 6 hours (also referred as Stage 1). In addition to the 3 stages of renal dysfunction, the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) criteria, unlike KDIGO includes 2 additional clinical outcomes of loss, indicating the complete loss of kidney function and end-stage renal disease, requiring renal replacement therapy [7-11].

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Table 1. The main causes of acute kidney injury

Factors	Causes
Prerenal factors - related to the decrease in blood volume	•Heart failure •Liver failure •Shock
Renal factors - related to damage to the glomeruli or the tubes leading from the glomeruli	•Infection •Cancer •Some medications •Nephrotoxins •Autoimmune diseases
Post renal factors - related to obstruction of the urine flow	•Cancers related to urinary tract •Prostate problems in men

Table 2. KDIGO, AKIN, and RIFLE criteria for acute kidney injury

Stage	Serum creatinine	Urine output
KDIGO criteria		
Definition of AKI: Increase in SCr ≥0.3 mg/dL within 48 h or ≥50% within 7 d		
1	•SCr ≥0.3 mg/dL within 48 h OR	
	•SCr to 1.50–1.99 times baseline over 7 d	•<0.5 mL/kg/h for 6-12h
2	•SCr to 2.00–2.99 times baseline	•<0.5 mL/kg/h for more than 12 h
3	• SCr to 3.00 times baseline -OR	
	•SCr increase to ≥4mg/dL	
	•Initiation of RRT	•<0.3 mL/kg/h for more than 24 h OR
	•Anuria for ≥12 h	
AKIN criteria		
Definition of AKI: Increase in SCr ≥0.3 mg/dL or ≥50% within 48 h		
1	•SCr ≥0.3 mg/dL SCr increase within 48h OR	
	•SCr to >1.5-2.0 times baseline	•<0.5 mL/kg/h for 6-12h
2	•SCr to >3-4 times baseline	•<0.5 mL/kg/h for more than 12 h
3	•SCr to >3 times baseline, OR	
	•SCr to >4 mg/dL with an acute increase of >0.5 mg/d OR	
	•Initiation of RRT	•<0.3 mL/kg/h for more than 24 h OR
	•Anuria for ≥12 h	
RIFLE criteria		
Definition of AKI: Increase in SCr ≥50% within 7 d		
Risk	•SCr ≥1.5x baseline increase within 7 d, sustained for ≥24h	•<0.5 mL/kg/h for more than 12 h
Injury	•SCr to ≥2x baseline increase	•<0.3 mL/kg/h for more than 24 h OR
	•Anuria for ≥12 h	
Failure	•SCr to >3x baseline increase OR	
	•SCr increase to ≥4 mg/dL (with increase of ≥0.5 mg/dL)	•<0.5 mL/kg/h for more than 12 h
Loss	•Complete loss of kidney function for >4 wk	
End stage	•Need for RRT for >3 mo	

AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease: Improving Global Outcomes; RIFLE: Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease; RRT: Renal replacement therapy; SCr, Serum creatinine.

The common point of these systems is the use of SCr level or the estimated glomerular filtration rate for classification. Although SCr is the gold-standard marker for renal function, SCr levels are related to age, sex, body muscle mass, dietary factors, and blood volume status. The use of glomerular filtration rate estimation was an attempt to overcome this issue [12-14]. SCr is not reliable in patients with sepsis, liver disease, muscle wasting, or fluid overload. Furthermore, it does not provide any information regarding the underlying etiology. Measurement of SCr concentration is an essential approach for the determination of

glomerular function. The SCr level also becomes very important when the kidneys have less than 50% of the nephron count. AKI may also be present with a normal creatinine level, if it is sufficiently elevated above baseline [15-19]. The "injury" label, which is now used instead of "failure," reflects different circumstances. "Failure" is associated with the loss of glomerular filtration ability of the kidney, whereas "injury" refers to pathologies before a decrease in glomerular filtration. Therefore, biomarkers that can demonstrate the damage before the glomerular filtration rate is affected would be very useful [20, 21].

Biomarkers for AKI

Within the past 20 years, several novel potential biomarkers (Table 3) have been studied in the urine or blood of AKI patients. The anatomical origins, physiological functions, kinetics, and release time of these markers in response to renal damage differ significantly [22-27]. The mechanisms associated with renal damage markers are:

1. Impaired filtration barriers
2. Reduced tubular reabsorption
3. Increased release of tubular proteins due to cell damage
4. Activation of inflammatory cells and release of activation products in response to injury

Urinary biomarkers are non-invasive, and easily measurable and obtainable in comparison with blood biomarkers. Different biomarkers are excreted in the urine according to the localization of the injury.

The secretion site of markers indicating acute renal injury are summarized below [22-23]:

Proximal tubules: Kidney injury molecule-1 (KIM-1), clusterin, neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor metalloproteinase 2 (TIMP-2), α-glutathione-S-transferase (α-GST), β-2-microglobulin, α-1 microglobulin, N-acetyl-β-D-glucosaminidase (NAG), osteopontin, urinary cystatin C, netrin-1, retinol binding protein (RBP), interleukin-18 (IL-18), hepatocyte growth factor (HGF), exosomal fetuin-A, liver-type fatty acid-binding protein (L-FABP), micro RNAs, insulin growth factor– binding protein 7 (IGFBP7), albumin

Glomerulus: Total protein, creatinine, cystatin C, β-2-microglobulin, podocalyxin, albumin

Distal tubules: Osteopontin, clusterin, NGAL, GST, L-FABP, calbindin D28

Table 3. Possible biomarkers for acute kidney injury

Indication of	Markers
Glomerular function	•Cystatin C •Neutrophil gelatinase-associated lipocalin •Retinol binding protein 4 •Hepcidin •Galectin-3 •Proenkephalin
Tubular function	•Cystatin C •Neutrophil gelatinase-associated lipocalin •Retinol binding protein 4
Renal inflammation	•Calprotectin •Interleukin-18
Damage	•N-acetyl-D-glucosaminidase[a]
[a]a cell cycle arrest marker	•γ-glutamyl transpeptidase[a]
[b]a nephrotoxicity marker	•Glutathione S-transferase[a]
	•Alanine aminopeptidase[a]
	•Lactate dehydrogenase[a]
	•Insulin-like growth factor-binding protein 7[b]
	•Tissue inhibitor of metalloproteinases-2[b]
	•Kidney injury molecule
	•Liver-type fatty acid-binding protein
	•Neutrophil gelatinase-associated lipocalin
	•Retinol-binding protein
	•Interleukin-18
	•α1/β2 microglobulin
	•MicroRNA, miRNA-201, and miRNA-21
	•Netrin-1
	•Clusterin

Table 4. Diagnostic and prognostic plasma and urine biomarkers for acute kidney injury

Diagnostic biomarkers for AKI	Prognostic biomarkers for AKI
Plasma or urinary NGAL	Plasma or urinary NGAL
Urinary KIM-1	Urinary KIM-1
Urinary L-FABP	Urinary L-FABP
Urinary IGFBP7	Urinary interleukin -18
Urinary TIMP-2	Urinary angiotensinogen
N-acetyl-βD-glucosaminidase	Urinary miRNA-210 and miRNA-21
Urinary interleukin-18	
Urinary calprotectin	
Urinary angiotensinogen	
Urinary miRNA-210 and miRNA-21	
β2 microglobulin	
α1-microglobulin	

AKI: Acute kidney injury; IGFBP7: Insulin-like growth factor-binding protein 7; KIM-1: Kidney injury molecule 1; L-FABP: Liver-type fatty acid-binding protein; NGAL: Neutrophil gelatinase-associated lipocalin; TIMP-2: Tissue inhibitor of metalloproteinase 2.

Collecting duct: Calbindin D28

Henle loop: Osteopontin

While excretion of high-molecular weight protein can be associated with glomerular injury, low-molecular weight proteinuria is associated with kidney tubulus damage. Some biomarkers reflect structural injury (KIM-1, NAG, NGAL, interleukin-8, TIMP-2, clusterin), some biomarkers are related to functional injury (cystatin C; total protein; albumin; β-2 microglobulin; urinary enzymes, such as NAG, cathepsin B, and β-glucosidase; brush border and tubular antigens; fetuin-A; type IV collagen; L-FABP; retinol binding protein 4; Tamm-Horsfall glycoprotein). NGAL and cystatin C are available in both serum and urine. While some biomarkers reflect reversible, functional change of the kidneys, the biomarkers associated with functional injury have been accepted as late biomarkers of kidney dysfunction [22-28].

What are the characteristics of the ideal marker for AKI?

The ideal biomarker for AKI would be an increase in a few minutes or hours after the onset of kidney failure and would remain elevated for as long as the kidney damage persists. The level would be quantitatively correlated with the level of kidney damage and decrease in proportion to kidney recovery [26]. Biomarkers for AKI have provided some benefits to the management of patients with AKI, and some are used routinely in the clinic [23]. NGAL, IL-18, KIM-1, L-FABP, TIMP-2, IGFBP7 and cystatin C are widely investigated biomarkers for AKI in clinical use. Characteristics of these biomarkers are summarized in Table 4.

NGAL, a lipocalin family protein, is a 25 kDa glycoprotein and is covalently bound to neutrophil gelatinase. It is expressed in lung, stomach, colon, and proximal tubular epithelial cells in humans and its expression is markedly increased in response to ischemic kidney or nephrotoxic injury [22-28]. Animal studies and cultured human proximal tubule cell studies have shown that NGAL could be an early marker for ischemia [29-31]. Furthermore, a meta-analysis of data indicated the importance of NGAL in the diagnosis and prognosis of AKI [32]. Therefore, there is strong evidence that urinary and serum NGAL levels are related to kidney injury in the early stages, and that NGAL may be a prognostic marker for AKI. Levels are associated with the need for dialysis and mortality. However, the secretion of NGAL from other tissues during periods of stress is an important disadvantage. It has been demonstrated that patients with several malignancies and patients with sepsis have higher plasma NGAL levels than healthy subjects, and that the level of urinary NGAL is elevated in patients with urinary tract infections [32]. NGAL binding to iron siderophore complexes (holo-NGAL) has bacteriostatic effects and it prevents uptake by bacterial pathogens [32, 33]. Holo-NGAL protects the kidney from ischemia-reperfusion injury, and its synthesis is induced by the kidney-protective enzyme heme oxygenase–1 [33]. It has been reported that the NGAL level increased 3 hours after injury, peaked after about 6 hours, and remained elevated for 5 days [34-36]. Additionally, an elevated plasma NGAL level is al¬so associated with chronic kidney disease [37].

KIM-1 is a 38.7-kDa type I cell membrane transmembrane tubular glycoprotein protein. Its intracellular domain is a signaling protein for tyrosine phosphorylation. The concentration of KIM is very low in normal kidney tissue and urine [22-26, 38]. After a proximal tubular kidney injury, the extracellular domain of KIM-1 is secreted from damaged cells into the urine in both rats and humans. After epithelial injury, remodeling of the epithelium and the removal of dead cells in the tubular lumen through phagocytosis are achieved by KIM-1. The results of animal studies indicated that urinary KIM-1 was a sensitive and specific marker of proximal tubular kidney injury, and that it increased earlier than common biomarkers (e.g., SCr or blood urea nitrogen) [37-45]. Therefore, KIM-1 has been thought to be a marker of kidney injury and that urinary KIM-1 could distinguish ischemic acute tubular necrosis from pre-renal azotemia.

IL-18 is a pro inflammatory cytokine. It is expressed in the cells of the distal tubule and the collecting tubule in the healthy kidney. Human studies show that IL-18 can serve as a marker for proximal tubular damage in acute tubular necrosis [46]. Additionally, it has been shown that IL-18 is a predictive biomarker of AKI after cardiopulmonary bypass, and that the use of both IL-18 and NGAL may be helpful in the management of patients with AKI after cardiopulmonary bypass, since these levels rise before that of SCr [47]. However, plasma IL-18 levels may be increased as a result of several conditions, such as endotoxemia, inflammatory diseases, and autoimmune diseases [48, 49]. Due to the fact that IL-18 is a proinflammatory marker, clinical evaluation of a high IL-18 level is problematic for AKI patients with sepsis. Therefore, the sensitivity and specificity of IL-18 for IKA are low [50]. As a result, the use of IL-18 in the management of AKI is limited.

L-FABP is a 14-kDa cytosolic protein synthesized by the liver, intestine, and proximal renal tubule epithelium [22-26, 51, 52]. It binds and carries long-chain fatty acids and protects from toxic cell effects by binding to lipid oxidation products. The human L-FABP gene contains a hypoxia responsive region and hypoxia induces L-FABP gene expression [53]. Studies show that L-FABP has antioxidant properties and that elevation in L-FABP expression was protective of the kidney against tubular injury and oxidative damage. [54-60]. Although urinary L-FABP has been accepted as an index marker of renal hypoxia, clinical trials are still limited and inadequate. Prospective studies including multiple causes of kidney disease are needed [51-61]. Nonetheless, L-FABP has already been approved for AKI as a diagnostic test in Japan [61].

Cystatin C is a cysteine protease inhibitor of low molecular weight. It is synthesized by all nucleated cells in the body [22-26]. Previous studies have indicated that cystatin C may be able to detect early changes in GFR more rapidly than SCr as the increase in the cystatin C level is faster and occurs earlier

than the increase in creatinine level in the patients with AKI [62, 63]. Cystatin C-based GFR estimation may be appropriate, especially in individuals with a very low SCr level (such as the elderly, children, renal transplant recipients, or malnourished patients) [62, 63]. Yet several fac¬tors, such as thyroid dysfunction, obesity, use of corticosteroids and inflammation agents, older age, male sex, and smoking have been found to be associated with an elevated serum cystatin C level; therefore, its use in AKI is limited [64-68]. Analytical techniques used to measure the cystatin C level have also been developed and immunonephelometric measurements of cystatin C level have become widespread. In a recently published meta-analysis, cystatin C was reported to be the best-performing marker in all clinical conditions associated with AKI in adults. [69].

TIMPs inhibit both matrix metalloproteinases (MMPs) and the proliferation of endothelial cells [22-26, 70, 71]. MMPs have several roles in tissue destruction, fibrosis, weakening of the matrix, and angiogenesis and apoptosis. Therefore, inhibitors of MMPs could have preventive effects in several diseases, such as cancer, neuroinflammatory diseases, atherosclerosis, or aneurysm [72]. TIMP-2 is a 21-kDa protein. TIMP-2 has both antiapoptotic and pro-proliferative effects, and it activates MMP-2, an enzyme that facilitates kidney recovery after ischemia-reperfusion injury [73]. Therefore, TIMP-2 has been identified as a strong predictor of development of kidney injury [74]. In contrast to proliferation inhibitory effects, some studies have shown that TIMP-2 promotes cellular proliferation [70]. Therefore, the importance of TIMP-2 levels in the clinical management of AKI is still unclear and additional studies are needed to define the role of TIMP-2 in kidney injury [74, 75].

IGFBP7 is a 29-kD protein. It is involved in tumor suppression and regulation of cellular aging through increasing the expression of p21 and p53 and inhibiting mitogen-activated protein kinase signaling [61, 71, 75, 76]. IGFBP7 is also an IGF-1 receptor antagonist. IGFBP7 secretion by injured tubular epithelial cells has been demonstrated. Therefore, it has been thought that elevated serum IGFBP7 levels may be associated with kidney damage through altering the hemodynamic properties of the kidney. Numerous studies are revealing the importance of IGFBP7 as an IGF-1 antagonist in the treatment of AKI [71, 77]. These studies are very important to demonstrate the usefulness of measuring the IGFBP7 level as an indication for IGF-1 treatment in AKI patients

Conclusion

Although some biomarkers are correlated with the severity of renal damage, and some biomarker combinations have predictive value for AKI, clinical trials are limited. Multicenter studies are needed to determine the best biomarkers or the best biomarker combination both for the screening and diagnosis of AKI and for the determination of the site of kidney injury. Another important limitation of biomarker research relates to the performance of biomarkers compared with that of SCr and oliguria, which are not renal-specific and are considered to be inadequate for the diagnosis of AKI. Analytical validation of these biomarker tests is also required. In the literature, there are different AKI definitions and different predictive values are given for markers. Cut-off values of these markers for the prediction of AKI are not yet available. Additionally, biomarker studies are based on en¬zyme immunoassays (ELISAs). ELISA methods produce quite different results depending on the reagent used and the duration of the test is very long. The major goal in AKI is to distinguish clinical outcomes by using biomarkers. The use of multiple biomarkers may be required in the management of patients with AKI. According to previous studies, NGAL, KIM-1, IL-18, cystatin C, TIMP-2, and IGFBP7 may be useful in the discrimination of AKI clinical outcomes. However, in order to determine the best combination of biomarkers in the management of AKI and to determine cut-off values of the biomarkers, multicenter studies are needed, as well as resolution of the analytical problems of these biomarkers and development and validation of the methods.

Conflict of interest: None declared.

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