Research Article

Biomarkers For Acute Kidney Injury

Mona M. Freiz; Ahmed A. Mohamed and Youssef I. Mousa
Department of Internal Medicine, Faculty of Medicine; Minia University, Egypt.

Abstract
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. 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.
Keywords: Acute kidney injury, physiological function, postrenal events.

Introduction
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 [1].

Several classification schemes have been proposed for patients with AKI according to the extent and duration of renal injury and to predict clinical outcomes. The classification sys tems contain criteria for serum creatinine (SCr) and urine out- put. 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 [1].

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 [2].

I- Biomarkers for AKI
Within the past 20 years, several novel potential biomarkers **(Table 1)** 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 [3].

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. [4]

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 Collecting duct: Calbindin D28 Henle loop: Osteopontin.

Table (1): 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

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 [5].

II- Advances in the Diagnosis and Treatment of Acute Kidney Injury in Cirrhosis Patients

Cirrhosis is a common clinical liver disease that is progressive and chronic. Due to the strong compensation ability of the liver, no apparent symptoms develop in the early stage. In contrast, multiple systems are affected in the decompensation stage. Acute kidney injury (AKI) is one of the most serious complications, especially in end-stage liver disease. AKI is characterized by a sharp drop in the glomerular filtration rate (GFR), a rapid increase in Scr and BUN, and increased sodium and water storage. [6].

The etiology of cirrhosis-related AKI is as follows:

(1) hypovolemia: an absolute shortage of blood volume, observed in conditions such as hemorrhage, diarrhea, excessive diuresis, and large-volume paracentesis; in contrast, a relative shortage of blood volume results from severe and unique cirrhosis-related abnormities of hemodynamics and nondiuretic, antihypertensive drugs; **(2)** inflammation: sepsis, including spontaneous bacterial peritonitis (SBP); **(3)** severe systemic response syndrome, which has separate causes; and **(4)** use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS), aminoglycosides, and radiographic contrast agents [7].

AKI develops in approximately 19% of hospitallized patients with cirrhosis[8]. It is important to make a definitive diagnosis in the early stage and to prescribe appropriate medications to avoid mortality and improve prognosis. It is also necessary to improve our knowledge and understanding of AKI and cirrhosis-related AKI.[3]

III- Diagnostic Criteria for AKI

AKI diagnosis is controversial due to a lack of unified diagnostic criteria[9], although some criteria, such as the RIFLE criteria, AKIN criteria, and KDIGO criteria, have been published. The Acute Dialysis Quality Initiative (ADQI) group first proposed the RIFLE diagnostic criteria in 2004.

On the basis of the RIFLE criteria, the Acute Kidney Injury Network (AKIN) criteria were established in 2007. Partly based on the AKIN and RIFLE criteria, Kidney Disease: Improving Global Outcomes (KDIGO) published the KDIGO standard for the evaluation and management of AKI in 2012.

RIFLE criteria include parameters present during the whole course of the condition, ranging from kidney injury to end-stage renal failure. The criteria divide AKI into three levels, namely, risk, injury, and failure, according to changes in Scr, GFR, and urine volume. The prognosis of AKI is classified into two levels, namely, loss of renal function and end-stage renal disease (ESRD), based on the time of complete loss of renal function [7].

IV- **Categories of Cirrhosis-Related AKI**

AKI can be divided into prerenal azotemia (PRA), acute tubular necrosis (ATN), and hepatorenal syndrome (HRS). Prerenal azotemia (PRA) results from various factors caused by the effective reduction of circulating blood volume. The reduction leads to a decrease in renal perfusion pressure.

Consequently, the GFR cannot be maintained at a normal level, but renal tissue integrity is not damaged. If risk factors are removed at an early stage, renal function can be reversed to normal in most patients. Acute tubular necrosis (ATN) results from renal tubular epithelial cell injury /necrosis caused by renal ischemia and/or toxic damage, which leads to a dramatic decline in GFR, severe electrolyte imbalance, water sodium retention, and metabolic acidosis. [10]

Type I: HRS is a special form of AKI and is one of the most serious syndromes of cirrhosis decompensation and acute liver failure [6].

V- Assessment of Renal Function

Traditional Markers Used to Assess Renal Function. Scr is the most practical and agreed upon biomarker for theugs, inflammation, assessment of renal function in cirrhosis patients[11], and it is the primary marker with which all types of renal failure can be predicted. However, there are some limitations to using Scr; namely, it may be normal or slightly increased because of high compensation and renal tubular secretion of creatinine in the presence of apparent kidney injury.

These factors can lead to a delay in obtaining the correct diagnosis and initiating early mana-

gement. Malnutrition exists in 67% of patients with cirrhosis, and production of creatinine from creatine decreases in muscles secondary to muscle wasting; therefore, Scr may be normal even if GFR is very low. The ability of this marker to assess renal function is much poorer.

GFR is currently the best indicator of renal function. Clinically, MDRD and the Cockcroft Gault formula are used to assess GFR in the general population. Nevertheless, both overestimate GFR in cirrhosis patients[12].

Furthermore, although MDRD has more advantages regarding its use in the assessment of GFR in cirrhosis patients, its accuracy is much lower than that in non-cirrhosis patients. The Cockcroft Gault formula is greatly influenced by weight, so it is not used for cirrhosis patients with edema and ascites[13].

Urine volume is a key marker for assessing kidney injury[7]. However, it is controversial to consider urine volume in patients with decompensated liver cirrhosis. Urine volume is affected by many factors, and its specificity is not high. For example, urine volume is normal in patients with nonoliguric AKI, despite the fact that their kidneys are severely damaged. Thus, urine volume has not been suggested for inclusion in the new ICA criteria for AKI diagnosis. [5].

References

1. Liu Y, Guo W, Zhang J, Xu C, Yu S, Mao Z, et al., Urinary interleukin 18 or detection of acute kidney injury: a meta-analysis. Am J Kidney Dis 2013;62:1058–67
2. Catania JM, Chen G, Parrish AR. Role of matrix metalloproteinases in renal pathophysiologies. Am J Physiol Renal Physiol 2007;292:F905–11
3. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). Best Pract Res Clin Anaesthesiol 2017;31:331–44.
4. Aregger F, Uehlinger DE, Witowski J, Brunisholz RA, Hunziker P, Frey FJ, et al., Identification of IGFBP-7 by urinary proteomics as a novel prognostic marker in early acute kidney injury. Kidney Int 2014; 85:909–19.
5. Koyner JL, Parikh CR. Clinical utility of biomarkers of AKI in cardiac surgery and critical illness. Clin J Am Soc Nephrol 2013;8:1034–42.
6. Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin. J. Am. Soc. Nephrol. 2006; 1:43–51
7. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, et al., Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005; 294:813–18.
8. Park KM, Byun JY, Kramers C, Kim JI, Huang PL, Bonventre JV. Inducible nitric-oxide synthase is an important contributor to prolonged protective effects of ischemic preconditioning in the mouse kidney. J. Biol. Chem. 2003;278:27256–66.
9. Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. Curr. Opin. Crit. Care. 2002;8:509–14.
10. Star RA. Treatment of acute renal failure. Kidney Int. 1998;54:1817–31
11. Emeigh Hart SG. Assessment of renal injury in vivo. J. Pharmacol. Toxicol. Methods. 2005;52:30–45.
12. Iqbal MP, Ali AA, Waqar MA, Mehboobali N. Urinary N-acetyl-beta-D-glucosaminidase in rheumatoid arthritis. Exp. Mol. Med. 1998;30:165–69.
13. Tominaga M, Fujiyama K, Hoshino T, Tanaka Y, Takeuchi T, et al., Urinary N-acetyl-beta-D-glucosaminidase in the patients with hyperthyroidism. Horm. Metab. Res. 1989;21:438–40.