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Role of renal biomarkers as predictors of acute kidney injury in cardiac surgery

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Abstract

Cardiac surgery is unique in using cardiopulmonary bypass in various clinical scenarios. Injury of vital organs is unavoidable in the perioperative period. Acute kidney injury is a consequence of the systemic inflammatory response after bypass, emboli, ischemia, and low cardiac output states, reportedly occurring in 30%–40% of open heart surgeries. Acute kidney injury is associated with increased morbidity, mortality, and cost. Many preventive measures (off-pump procedures, decreased crossclamp time, pulsatile flow, adequate hydration) are taken in the perioperative period to avoid organ injury, but in vain. Traditionally, blood urea, serum creatinine, and creatinine clearance rate were applied for prediction of acute kidney injury. The recent emergence of biomarkers such as neutrophil gelatinase-associated lipocalin, cystatin C, liver-type fatty acid binding protein, interleukin-18, kidney injury molecule-1, and tetrahydrobiopterin have helped in detecting acute kidney injury long before the rise of serum creatinine. These biomarkers can also be used as tools for predicting therapeutic effects in acute kidney injury and for monitoring drug toxicity. This review consolidates the knowledge of biomarkers and their application in acute kidney injury management.

Keywords

acute kidney injury, biological markers, cardiac surgical procedures, postoperative complications, predictive value of tests

Introduction

Acute kidney injury (AKI) is implicated as a major contributing factor to increased morbidity and mortality following cardiac surgery.[1–3] It occurs in 36% of patients undergoing cardiac surgery.[4,5] Serum creatinine or oliguria aid in diagnosing AKI. However, the influence of changes in muscle mass, tubular secretion, and numerous other nonrenal factors affect the serum concentration of creatinine, which limits its application as a predictor of AKI.[6] In spite of advances in management, AKI has shown disappointing outcomes in the past. Researchers have sought a biomarker for AKI, which might mimic troponin in sensitivity and specificity and can easily be used as a tool in clinical practice.[6] Modern technologies such as genomics and proteomics have encouraged the emergence of new biomarkers for predicting AKI in cardiac surgery as well as drug toxicity.[7]

Acute kidney injury

AKI is defined using serum creatinine and urine output criteria. The 2 most commonly used staging classifications are Risk-Injury-Failure-Endstage (RIFLE) and the Acute Kidney Injury Network criteria (AKIN).[8,9] RIFLE criteria have been used extensively in more than 2,500,000 subjects and validated to classify renal function.[10] A recent study has shown that RIFLE criteria

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Table 1. RIFLE (risk-injury-failure-loss-endstage) criteria for classification of acute renal failure.

Stage	Serum creatinine criteria	Urine output criteria
Risk	Serum creatinine 1.5 to $< 2.0 \times$ baseline	$<0.5\ mL{\cdot}kg^{-1}{\cdot}h^{-1} \times 6\ h$
Injury	Serum creatinine 2.0 to $< 3.0 \times$ baseline	$<0.5\ mL{\cdot}kg^{-1}{\cdot}h^{-1} \times 12\ h$
Failure	Serum creatinine $\geqslant 3.0 \times$ baseline	$<0.3\ mL{\cdot}kg^{-1}{\cdot}h^{-1} \times 24\ h$ or anuria $\times$ 12 h
Loss	Complete loss of kidney function >4 weeks	
Endstage	Endstage renal disease	

(Table 1) to be more acceptable and superior to the Acute Kidney Injury Network criteria for defining AKI in the first 48 h after surgery.[11]

Search for an ideal marker of acute kidney injury

Most current cardiological interventions are guided by serum cardiac enzymes because they predicted the onset of acute coronary syndrome. This has helped in early effective treatment. On the other hand, AKI diagnostic strategies such as blood urea, serum creatinine, atrial natriuretic peptide, and insulin-like growth factor-1 have failed to show a similar trend.[12–15] Results of perioperative sodium bicarbonate infusion to protect the kidney in cardiac surgery are conflicting.[16] N-acetyl cysteine has shown poor performance in preventing contrast-induced AKI.[17,18] Diagnostic mainstays such as the fractional excretion of sodium and urea have been repeatedly shown to be suboptimal in a variety of clinical settings, including cardiac surgery.[19–21] The traditional markers with the above-mentioned constraints have halted the possibility of new drug discovery. Such issues vary the outcome and increase the financial burden of clinical studies. The availability of ideal biomarkers would provide a tremendous impetus for development of new drugs to prevent AKI.

Assessment of biomarkers

The overall ability of a biomarker to predict at a variety of cut-off values is displayed graphically. The curve obtained is called a receiver operating characteristic (ROC) curve. The predictive ability of a biomarker is measured by the area under the ROC curve (AUC). ROC curves are used to define the specificity and sensitivity of a biomarker. A cut-off point closest to the upper left-hand corner of the ROC curve best differentiates disease from normal with the highest sensitivity and specificity. An individual biomarker with an AUC of 0.80 has a lower predictive power compared to a combination of patient data and other biomarkers, where the AUC is 1.0, as shown in Figure 1.[22]

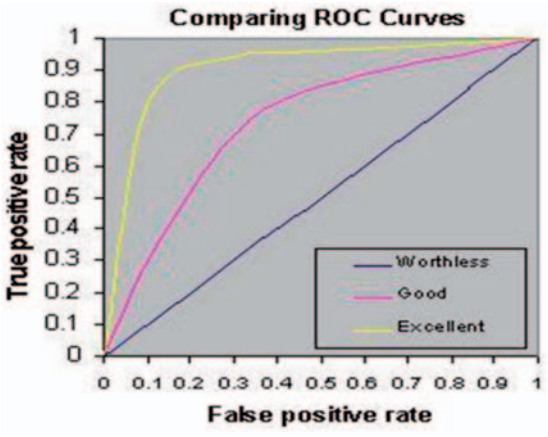

Figure 1. The best cutoff value is generally the point closest to the upper left corner of the receiver operating curve, which provides the highest sensitivity and specificity.

Promising biomarkers of acute kidney injury

Potential biomarkers of AKI with promising results include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CyC), liver-type fatty acid binding protein (L-FABP), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), tetrahydrobiopterin (BH4). NGAL and CyC are already being applied in clinical studies and have shown positive results. Biomarkers are studied in the serum and urine of patients. The sites of origin of these biomarkers are shown in Figure 2.

Neutrophil gelatinase-associated lipocalin

Human NGAL is a 25-kDa protein covalently bound to gelatinase from neutrophils. Principle organs expressing NGAL after epithelial injury are kidney, lung, stomach, and colon.[6] NGAL protein can be detected in blood and urine following tubular stress.[23,24] It has been detected in urine 2 h after

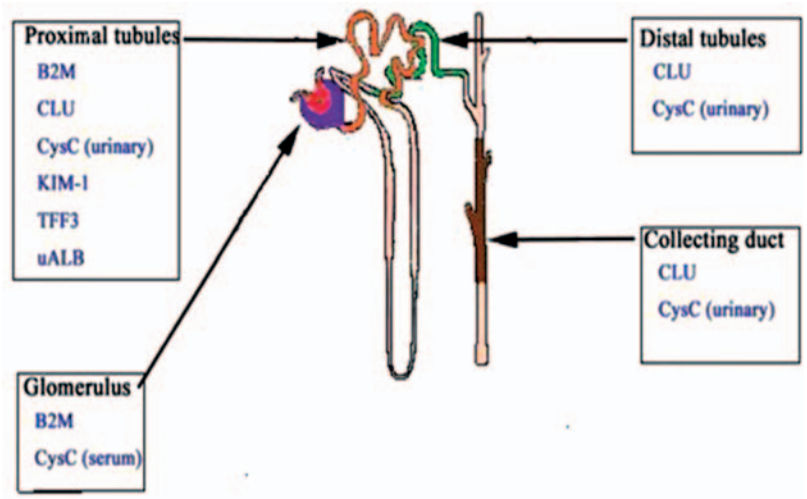

Figure 2. Illustration showing the origins of renal biomarkers from different parts of the nephron. μALB: urinary albumin; B2M: beta-2-microglobulin; CLU: clusterin; CysC: cystatin C; KIM-1: kidney injury molecule 1; TFF3: trefoil factor 3.

cardiopulmonary bypass (CPB).[6] Normal concentrations are 1.0 to 20 ng·mL^{-1} in urine (adults and children), and 70–105 ng·mL^{-1} (adults) or 30–80 ng·mL^{-1} (children) in serum.[7] Physiologic functions include an effective bacteriostatic action, antioxidant and iron-scavenging properties, and a growth factor-like action.[25,26] NGAL has drawn much attention recently, resulting in extensive studies worldwide. Nickolas and colleagues[27] studied urinary NGAL during hospital stay in 635 adults with various kidney diseases. NGAL was measured by an immunoblot technique. AKI was defined according to RIFLE criteria and was seen in 5% of subjects. Patients with AKI had significantly increased urinary levels of NGAL compared to those with other kidney diseases. A similar study was conducted by Wagener and colleagues[28] in 2008 who studied 426 patients during the first 48 h after cardiac surgery. AKI was defined as an increase in serum creatinine $\geqslant$50% or >26.5 μmol·L^{-1}. AKI was predicted in 20% of subjects. Another study in adults was conducted in the intensive care unit on patients with established AKI (defined as a 2-fold increase of serum creatinine in <5 days) secondary to ischemia, sepsis, or nephrotoxins. There was more than a 10-fold rise in plasma NGAL and a greater than 100-fold rise in urine NGAL by Western blot, compared to normal controls.[29] NGAL perhaps bears less predictive value in adults, with an AUC of 0.77–0.96.[30–33] Its predictive value increases with the severity of AKI.[34] Mishra and colleagues[35] studied 71 children undergoing CPB; 20 (28%) developed AKI. They observed a rise in urine NGAL from a mean of 1.6 μg·L^{-1} at baseline to 147 μg·L^{-1} after 2 h of CPB. Serum NGAL was increased from a mean of 3.2 μg·L^{-1} at baseline to 61 μg·L^{-1} 2 h after CPB. They found a significant correlation between AKI and the urine or serum concentrations of NGAL at 2 h after CPB. An AUC of 0.998 after 2 h for urine NGAL and 0.91 for plasma NGAL was established.

Interleukin-18

IL-18 is a proinflammatory cytokine that is induced and cleaved in the proximal tubule after AKI. The molecular weight of activated IL-18 is 18 kDa,[6] with plasma concentrations of 82·6–195·2 pg·mL^{-1} in adults.[36] IL-18 seems to be a reliable tool to differentiate acute tubular necrosis from other types of acute renal disease.[37] In some recent studies, urinary IL-18 was reported to predict AKI in patients undergoing renal transplant, critically ill children, and after pediatric cardiac surgery.[37–39] Parikh and colleagues,[39] in a study on 55 pediatric cardiac surgery patients, found that urinary IL-18 increased 4–6 h after CPB, peaked to 25-fold at 12 h, and remained markedly elevated up to 48 h after CPB. The first clinical study in adult cardiac patients by Haase and colleagues[40] concluded that urinary IL-18 may be a marker of CPB-associated inflammation. Further clinical studies are needed to establish its role as a lone biomarker for AKI.

Cystatin C

CyC is an endogenous cysteine proteinase inhibitor with a molecular weight of 13 kDa. Nucleated cells are the source of secretion. The normal serum CyC concentration is 0.8–2.04 mg·L^{-1}.[41,42] Whereas plasma CyC is used to estimate glomerular filtration rate, urine CyC is a biomarker of tubular cell integrity. Anthropometric measurements, inflammatory processes, corticosteroids, as well as changes in thyroid function affect CyC levels.[43] Plasma CyC can be used

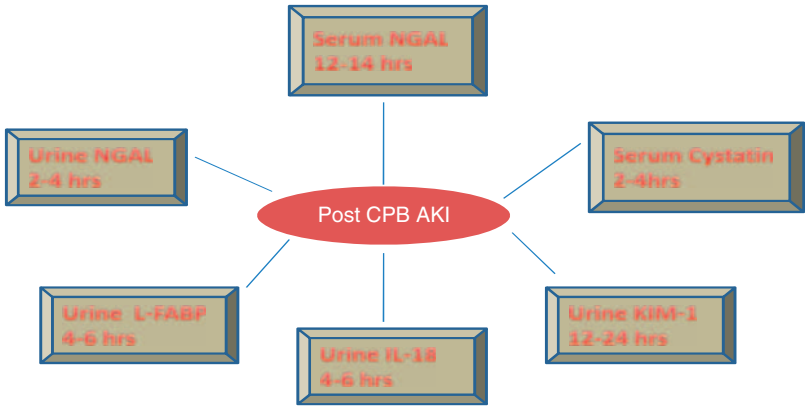

Figure 3. Post-cardiopulmonary bypass detection of urinary biomarkers. AKI: acute kidney injury; CPB: cardiopulmonary bypass; L-FABP: liver-type fatty acid binding protein; IL-18: interleukin-18; KIM-1: kidney injury molecule 1; NGAL: neutrophil gelatinase-associated lipocalin.

to predict the onset of AKI and the need for renal replacement therapy.[44,45] Two recent studies could not show superiority of CyC over serum creatinine, whereas many other studies have.[46–50] It is more sensitive for reduced glomerular filtration rate than kidney injury. This limits its use to differentiate various types of AKI. It can easily be measured by a standardized immune nephelometric assay.[6]

The time of detection of biomarkers according to their appearance in urine and serum is shown in Figure 3. Urine NGAL and serum CyC levels can be estimated as early as 2–4 h after cardiac surgery. The ease of sample collection and early detection have encouraged there usage in clinical studies.

Liver-type fatty acid binding protein

L- FABP is a 13.5 kDa protein and renal L-FABP is found in the cytoplasm of proximal tubules.[7] Normal concentrations in urine are <10 µg per g of creatinine in children and 5–20 µg per g of creatinine in adults.[51,52] It helps to maintain low levels of free fatty acids in the cytoplasm.[53] It binds selectively to intracellular free unsaturated fatty acids and lipid peroxidation products during hypoxic tissue injury. Recent studies have shown that urinary L-FABP is an early marker of AKI due to acute tubular necrosis, sepsis, cardiac surgery, nephrotoxins and radiocontrast agents, differentiating patients with septic shock from those suffering from severe sepsis or established renal injury and normal controls.[52,54–56] AKI is best predicted by urinary L-FABP, and may help in dialysis-free survival assessment.[57] Urine L-FABP is found to rise exponentially and earlier than serum L-FABP in contrast-induced nephropathy in mice and post-cardiac pediatric patients, with an AUC of 0.81 at 4 h.[58] Compared to NGAL, L-FABP was found to rise later in AKI, and future clinical studies are required to establish its predictive role.

Kidney injury molecule-1

KIM-1 is a glycoprotein that is expressed after ischemic and nephrotoxic injury to the proximal tubule cells.[6,59] It helps to distinguish between ischemic AKI from prerenal azotemia and chronic kidney disease.[60] Huo and colleagues[61] hypothesized that in the initial stage of renal injury, KIM-1 plays a protective role, and a damaging role in the later stage due to the excessive cell proliferation caused by KIM-1-induced renal repair. Han and colleagues[60] studied the KIM-1 levels in 40 patients and found that the mean level was increased to $63.0 \pm 4.7\ \text{ng}\cdot\text{mL}^{-1}$ in AKI compared to a normal value of $38.9 \pm 1.3\ \text{ng}\cdot\text{mL}^{-1}$. In a case control study, an AUC of 0.83 for KIM-1 was found for the diagnosis of AKI at 12 h after CPB.[62] Its role in predicting AKI is limited due to delayed elevation (12–24 h), however, its combination with other biomarkers has increased its applicability.[6]

Surrogate biomarkers

A study was conducted in 90 adult cardiac surgery patients using urinary biomarkers KIM-1, N-acetyl-beta-D-glucosaminidase, and NGAL.[63] The AUC values to predict AKI immediately and 3 h after the operation were 0.68 and 0.65 for KIM-1; 0.61 and 0.63 for N-acetyl-beta-D-glucosaminidase; and 0.59 and 0.65 for NGAL. The combination of the 3 biomarkers enhanced the sensitivity of early detection of postoperative AKI with an AUC of 0.75 immediately and 0.78 after 3 h.[63] Vaidya and colleagues[64] conducted a study on 204 patients who were divided into study and control groups of 102 patients each.

Table 2. Potential future biomarkers.

Biomarkers	Clinical significance	Nephron segment	Comments
Albumin	Nephrotoxic, ischemic or septic AKI	Glomerulus and proximal tubule	Increased urinary excretion may reflect alterations in glomerular permeability and/or defects in proximal tubular reabsorption. Nonspecific biomarker
Alpha-glutathione s-transferase	Nephrotoxic, septic, or ischemic AKI or renal transplantation	Proximal tubule	Clinical data are limited
Alpha-1-microglobulin	Nephrotoxic, ischemic, or septic AKI or renal transplantation	Proximal tubule	Lack of standardized reference levels. Nonspecific
Beta-2-microglobulin	Nephrotoxic, ischemic, or septic AKI or renal transplantation	Proximal tubule	Clinical applicability limited by instability in urine
Clusterin	No AKI clinical studies to date	Proximal and distal tubules	Increased urinary levels observed in rat models of tubular proteinuria
Cysteine-rich protein	Ischemic AKI	Proximal tubule	Urinary levels do not reflect progressive injury; levels assessed via immunoblotting
Heart-type fatty acid-binding protein	Nephrotoxic AKI or renal transplantation	Distal tubule	Increased urinary levels in the setting of heart disease may limit specificity
Hepatocyte growth factor	Nephrotoxic, ischemic, or septic AKI or renal transplantation	Proximal and distal tubules	Urinary levels may predict adverse outcomes (death or RRT)
N-Acetyl-β-glucosaminidase	Nephrotoxic, ischemic, or septic AKI or renal transplantation	Proximal tubule	Levels may predict adverse outcome (death/RRT). Nonspecific
Netrin-1	Nephrotoxic, ischemic, or septic AKI	Proximal tubule	Limited clinical data
Osteopontin	No AKI clinical studies to date	Proximal tubule, loop of Henle and distal tubule	Increased urinary levels observed in rat models and humans following nephrotoxicity
Retinol-binding protein	Nephrotoxic, ischemic, or septic AKI or renal transplantation	Proximal tubule	Decreased sensitivity in vitamin A-deficient states
Sodium/hydrogen exchanger isoform 3	Nephrotoxic, ischemic, or septic AKI or renal transplantation	Proximal tubule and loop of Henle	Levels assessed via immunoblotting
Others			
Trefoil factor 3			
Aprotinin			
Tetrahydrobiopterin			
Matrix metalloproteinase-9			
Alkaline phosphatase			
Gamma-glutamyl transpeptidase			
Pi-glutathione s-transferase			

AKI: acute kidney injury; RRT: renal replacement therapy.

Nine biomarkers (KIM-1, NGAL, IL-18, hepatocyte growth factor, CyC, N-acetyl-beta-D-glucosaminidase, vascular endothelial growth factor, chemokine interferon-inducible protein 10, and total protein) were studied for predicting AKI. The study concluded that KIM-1, NGAL, hepatocyte growth factor, and total protein were the 4 best performers individually as well as in combination, with a greater AUC (0.94) compared to any individual biomarker.[64] NGAL and CyC in combination have been shown to be independent predictors of the duration and severity of AKI after adult cardiac surgery.[29] Confirmation of the utility of surrogate biomarkers in future prospective studies will help in their clinical application. Emerging biomarkers with the potential for better prediction are undergoing clinical trials, and are shown in Table 2.[22,65–70]

Conclusion

Novel biomarkers have shown great promise and stimulated much interest in their validation and adoption in clinical scenarios. The specificity of these biomarkers in differentiating types of AKI has yet to be established. Combinations of some biomarkers have increased the sensitivity and specificity for predicting AKI, and have overcome the limitations of individual biomarkers. Since AKI imposes great challenges to surgeons in intensive care unit settings, it should be diagnosed within 1 h so that immediate specific therapy can be commenced. Biomarkers might also generate tremendous interest in developing new management strategies for AKI in patients undergoing cardiac surgery.

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Conflict of interest statement

None declared

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