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EARLY BIOMARKERS IN ACUTE KIDNEY INJURY- A REVIEW

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ABSTRACT

AKI Acute kidney injury (AKI) is a commonly observed pathological condition with an increased rate of mortality, a heavy burden of illness and eventually economic burden. AKI is a frequent complication in several clinical settings, including large surgeries, emergency departments, and intensive care units. Once AKI occurs, the requirement for renal replacement therapy, persistent renal dysfunction, dialysis, and mortality increases. kidneys are unable to generate new nephrons, and maladaptive or repeated episodes of AKI will lead to further nephron loss and injury that is ultimately associated with chronic kidney disease and end-stage renal disease. A number of several novel biomarkers in plasma and urine have been investigated to improve the risk prediction of AKI. This systemic review comprehensively collected information on novel biomarkers like Serum creatinine, Serum Albumin, Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor–binding protein 7 (IGFBP7), Neutrophil gelatinase-associated lipocalin, Cystatin C, kidney injury molecule-1, Monocyte chemotactic peptide-1, Urinary N-acetyl- β -D-glucosaminidase and β_2-microglobulin, Alpha-1 Microglobulin, Urinary interleukin-18, Urinary liver-type fatty acid-binding protein level, Netrin-1, Endogenous Ouabain, Selenium binding protein-1, IL-6, BPI fold- containing family a member 2, microRNAs, Lanosterol Synthase Genetic Variants , Semaphorin 3A , Soluble urokinase receptor, Urinary Retinol Binding Protein, kininogen 1, Sodium/hydrogen exchanger isoform 3, Dickkopf-3, Hepatocyte Growth Factor, Tretolin Factor 3, Glutathione S transferase and Proenkephalin.

KEYWORDS: Acute kidney injury; Early biomarkers; Detection site for renal damage; chronic kidney disease

1. INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in several clinical settings, including large surgeries, emergency departments, and intensive care units. Once AKI occurs, the requirement for renal replacement therapy (RRT), persistent renal dysfunction, dialysis, and eventually mortality increases.[1] In view of these conditions, a number of studies have focused on early detection of renal damage for early intervention, and thereby decrease in morbidity and mortality of AKI.[2] It has been reported that kidneys can regenerate provided intensity of damage is not very high. However, kidneys are unable to generate new nephrons, and repeated episodes of AKI will lead to further nephron loss and injury that is ultimately associated with chronic kidney disease (CKD) and end-stage renal disease (ESRD).[3,4] Pathways of AKI damage is increasingly better understood. These pathways include ischaemia, inflammation, tubular epithelial cell loss, and early initiation of interstitial fibrosis; the role of epithelial cells is increasingly recognized.[5]

A number of several novel biomarkers in plasma and urine have been investigated to improve the risk prediction of AKI.[6] There is already a report on seven urinary nephrotoxic biomarkers, including total protein, albumin, kidney injury molecule-1, clusterin, β_2-micro-globulin, cystatin C and trefoil factor 3, for particular uses in regulatory decision-making. Moreover, Microalbumin (Low Molecular Weight Protein) has been also recognized as a novel nephrotoxic biomarker.[7] The lack of early biomarkers for AKI has limitation for better quality life. AKI might also lead to increased death amongst patients as established biomarkers for the assessment of the severity of the renal disease are not available. The conventional biomarkers for renal disease lack in specificity and sensitivity and therefore exact diagnosis for renal injury is not possible that may delay in timely treatment.

The severe consequences of AKI urgently need some options for early detection. This systematic review comprehensively collected information on the early biomarkers. Some main novel AKI biomarkers are listed (table 1& fig1) with their site of release and discussed below.

2. Serum creatinine (Scr)

Basically, creatinine levels may be unreliable because creatinine production is reduced when the patient becomes hypothermic as a consequence of decreased blood flow, or levels may be increased because of muscle damage during surgery. As such, SCr increase or decrease in glomerular filtration rate are initially masked by a compensatory improved renal function, it

cannot be considered an early marker of AKI and cannot be used to timely set effective therapies to treat AKI in patients during phases when the injury is still potentially reversible.[7] AKI is typically defined on the basis of the Acute Kidney Injury Network (AKIN) criteria where stage I AKI is ≥50% increase in baseline serum creatinine, ≥0.3 mg/dl increase in baseline serum creatinine, or urine output <0.5 cc/kg/h for 6 h. Stage II AKI is defined as at least a doubling of the serum creatinine from the baseline value or urine output <0.5 cc/kg/h for 12 hours. Stage III AKI is at least a tripling of serum creatinine from the baseline value, urine output <0.3 cc/kg /h for 24 h, anuria for 12 h, or patients who receive dialysis. Although a decrease in urine output is a part of the AKIN criteria, most clinical research studies only use increases in serum creatinine to define AKI. Serum creatinine often rises without intrinsic kidney injury and does not always rise with intrinsic kidney injury.[9]

3. Scope of novel biomarkers of AKI

3.1. Tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7)

Urinary [TIMP-2]· [IGFBP7] is reported as an important biomarker for understanding early damage of the kidney.[6] Although, number of studies have reported certain advantages and limitations associated with its use so the clinicians must be aware of those aspects during their patient handling.[9] This biomarker has shown a very good profile of accuracy and stability in patients having more comorbidities. US FDA have approved the use of the TIMP-2 and IGFBP7 ([TIMP-2] × [IGFBP7]) product which is also labelled as cell cycle arrest biomarkers for use in very severe condition of patients by nephrologists in the early prediction of AKI in the critical care setting.[10] Nephrocheck® is the only commercially available test for [TIMP-2] × [IGFBP7] which has been allowed by the FDA for risk assessment of moderate to severe AKI in critically ill patients. The approved test is an in-vitro diagnostic device that quantitatively measures IGFBP7 and TIMP-2 in human urine by fluorescence immunoassay on the ASTUTE140® Meter.[11] TIMP-2 and IGFBP7 are recent promising markers for identification of cardiac surgery-associated –AKI.[12]

3.2. Neutrophil gelatinase associated lipocalin (NGAL)

NGAL is again very important biomarker for early detection of kidney damage. It has been reported in AKI patients that NGAL levels significantly increase 24-48 h before the actually detectable serum Cr levels. It`s expression is normally released from the thick ascending limb and the intercalated cells of the thick collecting duct of the kidney. Some NGAL expression

is also present in the proximal tubular epithelium, once NGAL is filtered by the glomerulus and reabsorbed by the proximal tubule in a megalin-dependent manner.[13] It mainly plays a vital role in the regulation of cell proliferation, repair processes, and tubular reepithelization. NGAL expression corresponds to an additional iron transport pathway, which increases the transcription of hemeoxygenase, an enzyme with proliferative and antiapoptotic effects that protects and preserves proximal tubular cells.[14,15] Several biological functions for NGAL have been suggested; in the kidney, NGAL release is associated with ischemic or nephrotoxic insults. Further, decrease in tubular reabsorption of NGAL after AKI might result into an increase in its concentration in the urine, that in turn acquires a status of the "troponin" of the kidneys.[16] And thus, its release mainly from the distal tubule has been associated with an increase in kidney injury.[17] Newer findings also suggest that measurements of urinary NGAL levels in cardiac patients of post-surgery AKI might be at benefit for an early diagnosis and thereby permitting clinicians to decide for right therapeutic management that have the potential to reverse renal cellular damage and minimize further kidney injury.[18] It is considered to be the promising biomarker and has a good outcome in various clinical settings like cardiopulmonary bypass. It has also shown promising results with less studied biomarkers for the prediction of AKI in children, including TIMP2, IGFBP7, uromodulin, tumour necrosis factor-α and IL-8.[19] There is a report for the use of NGAL with reference to the AKI`s early prediction and prognosis of AKI has been established in three clinical settings like cardiac surgery, critical illness and kidney transplantation. Based on several studies that strongly support the use of NGAL as a biomarker for the prediction of AKI [20]. In addition to above, NGAL plays a vital role in the regulation of cell survival and cell proliferation. The expression of NGAL in proliferating and regenerating tubular epithelial cells indicates its role in the process of repair.[21]

3.3. Cystatin C (CYsC)

CysC, a low molecular-weight protein measurable in blood and freely filtered by the glomerulus, is considered to be less affected by age and gender. It has been reported that in the patients of AKI serum CysC rises well before the rise in SCr, revealing CysC as an "early AKI biomarker".[22] CysC has been proposed as an alternative to SCr for estimating glomerular filtration rate (GFR), for years. Serum CysC provides early prediction of renal dysfunction in ACLF (Acute-on-chronic liver failure) patients with a normal serum Cr level. It has been well established that severe renal dysfunction is observed in patients with acute-on-chronic liver failure (ACLF) due to inflammation and circulatory abnormalities. So, CysC

might be of use for early detection of renal damage in patients with ACLF as compared to any increase in serum Cr levels. In China, hepatitis B virus (HBV)-infected ACLF patients account for > 80% of ACLF patients, due to a high incidence of chronic HBV infection.[3] Kidney dysfunction is a common complication of advanced liver disease and associated with a high mortality. Unlike Cr level, CysC level is independent of muscle mass, age or sex, and is not influenced by inflammatory conditions or malignancy.[3] CysC is currently being investigated for the prediction of AKI in patients with cardiac surgery, advanced liver diseases, and patients undergoing liver transplantation. Several studies have reported that CysC is more useful for the assessment of renal function in patients with cirrhosis.[23] In children with chronic kidney disease, CysC is a more accurate marker of glomerular filtration rate (GFR).[24,25] Several studies have used CysC rise as a renal outcome.[26] The global availability of standardized clinical platforms for the measurement of S CysC[27,28], as well as other promising AKI biomarkers such as neutrophil gelatinase-associated lipocalin[29] that indicate structural renal injury, potentially bring us closer to a personalized and predictive approach to the diagnosis and management of community-acquired AKI. Cystatin C can be used for the early predicion of AKI with COVID-19 patients.[30]

3.4. Kidney injury molecule-1 (KIM-1)

KIM-1, a recently discovered transmembrane protein, is expressed in dedifferentiated proximal renal tubular epithelial cells in damaged regions. It may participate in the progress of renal injury or repair. A soluble form of human KIM-1 can be detected in the urine of patients with ATN (acute tubular necrosis) and may serve as a useful biomarker for early renal tubule injuryrevealing the early diagnosis.[31] It mediates epithelial phagocytosis in the injured kidney converting the proximal epithelial cell into a phagocyte, with potentially important pathophysiological implications for modulation of the immune response and repair process after injury.[32] Preclinical and clinical studies reports that urinary KIM-1 is a sensitive and specific biomarker for various forms of nephrotoxic injury, cardiac surgery-induced kidney injury, transplant rejection etc.. KIM-1 performs epithelial phagocytosis leading to repair process. KIM-1 serves as a highly sensitive and specific urinary biomarker for kidney injury and may also be a therapeutic target for various kidney diseases.[32] It is a type-1 cell membrane glycoprotein up-regulated in dedifferentiated proximal tubule epithelial cells.[33] Similar to NGAL, its expression levels are also up-regulated in the kidney proximal tubule cells following ischemic injury.[34]

3.5. Monocyte chemotactic protein-1 (MCP-1)

MCP-1 could be used as a biomarker to identify high-risk patients for potential AKI prevention strategies in the setting of cardiac operations.[35] It has been reported that, urinary epidermal growth factor (uEGF)/MCP-1 has a better ability to predict the composite endpoint and correlates more closely with kidney function decline in advanced diabetic kidney disease (DKD) as compared to uEGF/Cr or uMCP-1/Cr alone.[36] MCP-1 can be measured and used for the prediction of AKI with upper urinary tract obstruction patients. expression levels are also up-regulated in the kidney proximal tubule cells following ischemic injury.[33]

3.6. Urinary N-acetyl-β-D-glucosaminidase (uNAG)

Urinary N-acetyl-β-D-glucosaminidase represents tubular damage. NAG presented as a promising marker of impending AKI and the necessity of renal replacement therapy.[37] Deng et al. reported that combination of functional and tubular damage biomarkers improves the predictive accuracy for AKI after resection of intracranial space-occupying lesions.[38] Moafi et al. conducted a study in 2020 for the assessment of acute kidney injury by urinary β2-MG and NAG in pediatric cancer patients prescribed with cisplatin, carboplatin, and ifosfamide by measuring urinary β2-MG, urinary NAG, blood urea nitrogen , serum and urinary Cr and they concluded that Urinary β2-MG, urinary β2-MG/Cr, and NAG/Cr are significant biomarkers than serum Cr in earlier diagnosis and treatment of AKI in cancer patients.[39]

3.7. Alpha-1 Micro globulin

This biomarker is reported to be used in the detection of AKI in HIV infection.[40]

3.8. Urinary IL-18

Both urinary interleukin-18 and cystatin-C are independently predictive of AKI in non-septic critically ill neonates.[41] It is shown that, urinary IL-18 s found 48 h earlier in patients with AKIand acute respiratory distress syndrome.[42] IL-18, an anti-inflammatory cytokine that is initially synthesized passively (24 kDa) and subsequently is activated by caspase-1. It has been reported that, the urinary concentration of IL-18 rises as the AKI patient`s condition worsens. Compared to other biomarkers, this marker is not considered a strong primary predictor.[43]

3.9. Urinary liver type fatty acid binding protein level (uL-FABP)

Urinary L-FABP reflects renal tubular injury. Urinary L-FABP levels are markedly upregulated in the proximal tubules after renal ischemia.[44] It appears to be a sensitive

biomarker of AKI in patients undergoing abdominal aortic repair.[45] It has been described that upon detection of lipid peroxidation increments, a hypoxia-responsive element upregulates L-FABP synthesis, which then allows binding of lipid peroxides for their urinary excretion and both expression and urinary excretion of L-FABP have been shown to be increased under tubular hypoxic conditions. kidney tubular epithelial cells are very rich in mitochondria; therefore, they are particularly vulnerable to hypoxic challenge. It is suggested that L-FABP might prove an important biomarker for a graft tissue insult.[46] Thus, novel renal tubular biomarkers such as uL-FABP, may offer an alternative approach for the diagnosis of AKI.

3.10. Netrin-1

Kidney has one of the highest levels of netrin expression.[47] Studies demonstrate that semaphorin 3A and netrin-1 can be useful early diagnostic biomarkers of AKI after liver transplantation.[48] So far, there is no evidence of good marker for early kidney injury in premature new-borns. In present situation, netrin-1 seems to be a promising biomarker for such type of kidney damage in various pathological conditions. The netrin-1/creatinine ratio is increased in premature babies.[49]

3.11. Endogenous Ouabain (EO)

EO is reported to be a neuroendocrine hormone which might help to understand condition of a critically ill patients suffering from AKI. It is considered a stress hormone which is secreted from the the adrenal gland since a) rats preexposed to acute swim stress shows significant increased levels of EO in plasma and adrenal glands; b) marked and rapid increases of plasma EO in humans during physical exercise have been reported; c) about 50% of humans with untreated essential hypertension have significantly elevated plasma EO that correlates directly with blood pressure (BP); d) increased circulating EO has been related to cardiomyopathy and decreased renal function.[50] It has been found elevated in a large proportion of critically ill patients. The occurrence of these substances is associated with increased morbidity and hospital mortality rates. EO, contributes to renal failure and may be linked to cardiomyopathy in chronic kidney disease so it seems to be a valuable biomarker of heart failure.

3.12. Selenium binding protein-1 (SBP-1)

Recently, a new biomarker, SBP1, was identified for detection of nephrotoxicity using proteomic analysis. It is suggested that SBP1 may play a critical role in the pathological processes underlying chemical-induced nephrotoxicity. It is suggested that Urinary excretion of SBP1 can be considered as a a sensitive and specific biomarker to diagnose early kidney injury.[51]

3.13. Can IL-6 act as an early biomarker for AKI in COVID-19 patient?

Severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) is the pathogen responsible of atypical pneumonia that has affected more than 330,000 people and caused death of more than 14,000 patients (as of March 23, 2020, WHO Report). Interestingly, about 25% of AKI occurrence has been reported in this clinical setting.[52,53]

As per literature till date, the prevalence of AKI amongst patients with COVID-19 is less. Although the mechanisms of the involvement of kidney can be understood by dividing into three aspects: cytokine damage, organ crosstalk and systemic effects. Cytokine release syndrome (CRS) or 'cytokine storm', can occur in various conditions including sepsis, haemophagocytic syndrome and chimeric antigen receptor (CAR) T cell therapy.[54] Among patients with COVID-19, the plasma concentration of IL-6 (cytokine)is increased in those with ARDS.[55] Extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation and continuous kidney replacement therapy (CKRT) can also contribute to cytokine generation. The anti-IL-6 monoclonal antibody tocilizumab is widely used to treat CRS in patients who have undergone CAR T cell therapy[54] and is now also being used empirically in patients with severe COVID-19. Increase in anti-inflammatory mediators can cause a state of immunosuppression in patients. In these circumstances, specific conditions (such as shock-like syndrome, the need for vasopressors and capillary leak syndrome) and laboratory criteria (such as the levels of IL-6 and other cytokines as well as cell cycle arrest biomarkers with high predictive value for AKI such as [TIMP2] *[IGFBP7]) could represent objective and standardized criteria to guide therapy.[56]

3.14. BPI fold containing family a member-2 (BPIFA2)

Kota *et al.* have reported that BPIFA2 can be detected in `stress` or `damaged` status of kidney in AKI patients.[57] They have furnished ample and well-documented molecular, genetic, and clinical proof to adopt BPI fold-containing family A member 2 (BPIFA2) as a novel sensitive AKI biomarker. It is also stated that BPIFA2 expression was observed early

in both murine and human kidneys and therefore BPIFA2 protein could be easily detectable in plasma and urine of the AKI patients. In clinical practice, however, sensitive biomarkers are of crucial importance for early detection and monitoring of sepsis-induced AKI. Sepsis is characterized by a dysregulated immune-inflammatory host response to infection resulting in life-threatening organ failure.[58] Up to 50% of patients with severe sepsis and septic shock develop AKI.[59] AKI more likely has a functional (glomerular) rather than an injurious (tubular) origin.[60] The BPIFA2 forms identified in circulation have a MW of 15 and 18 kDa[57] and thus might work as sensitive biomarker.

3.15. MicroRNAs in kidney

There is very little knowhow about circulating miRNAs for their role as biomarkers in AKI. miRNAs have started to emerge as key players in many relevant diseases, including nephropathies.[61] Recently, study shows that Urinary microRNAs miR-15b and miR-30a used as novel non-invasive biomarkers for gentamicin-induced acute kidney injury.[62]

3.16. Lanosterol synthase genetic variants & EO against kidney damage

EO (steroid hormone) is produced from a pathway involving lanosterol synthase (LSS), an enzyme plays an important role in the synthesis of cholesterol.[63] LSS catalyses the cyclization of oxidosqualene in lanosterol, a precursor of steroid hormones.[64,65] Rossella latrine et al. have recently proposed EO, an adrenocortical cardiac glycoside and well-known effector of hypertension-mediated cardiovascular damage, as a new "predisposing" biomarker of AKI in humans.[64] Elevated EO levels cause glomerular damage in rats and podocyte cell cultures, and elevated circulating EO levels are associated with lower GFRs. Moreover, it has been reported that the LSS gene is transcribed at certain nephron sites. LSS rs2254524 A allele may represent a starting point for EO-mediated kidney injury, as well as being a genetic background that can predispose to the development of kidney failure. The rs2254524 A allele has also been shown to influence EO synthesis in transfected cells.[64]

3.17. Semaphorin 3A (Sema 3A)

Sema 3A is the secretory proteins that belongs to a family of axon-directed factors found in podocytes, distal tubules, and collecting tubes of the kidney. It is reported as a promising target protein that is involved in the mammalian target of the rapamycin (mTOR) pathway in renal damage but it has an unknown role in the course of hexavalent chromium-Cr (VI)-induced nephrotoxicity. The discovery of new biomarkers for early detection of drug-induced acute kidney injury (AKI) is clinically important.[66] Sema 3A plays a vital role in

inflammatory processes which lead to tubular damage and also involved in epithelial repair processes that is needed for the repair of the kidney function. SEMA3A is localized in the distal tubules of the mice. The SEMA3A expression is found increased in both kidney and serum. semaphorin-plexin pathway represents a new and promising pharmacological target in kidney diseases.[67]

3.18. Soluble urokinase receptor (suPAR)

A recent study reports that increased plasma levels of suPAR are associated with the development of AKI.[68] Furthermore, murine experiments demonstrated that suPAR might sensitize the kidney to the deleterious effects of nephrotoxic insults. These findings suggest that suPAR could represent a new category of AKI biomarker that is increased prior to AKI, predicts increased risk of AKI and has a pathogenic role in the development of AKI. It is suggested that suPAR might sensitize the kidney to subsequent injury by altering proximal tubular mitochondrial energy metabolism (towards increased energy production and oxygen consumption) and increasing oxidative stress.[69]

3.19. Urinary retinol binding protein (uRBP4) and kininogen-1

uRBP4 is very specific and sensitive biomarker for evaluating loss of function of the human proximal renal tubule. Assessment of uRBP4 is recognised as an excellent screening test for renal fanconi syndrome (RFS). It is established biomarker for gentamicin -induced toxicity.[70] Patient's recovery can be predicted by measuring RBP4and establishing a role of RBP4 in prognosis assessment. In an end stage renal disease (ESRD) mouse model, KNG1and RBP4 genes are two of the best kidney up-regulated ones. Kininogen is a wellknown precursor for kinins. During the process, the serine protease kallikrein processes kininogen to produce bradykinin like peptides that regulates blood pressure, renal, cardiac function and inflammation in addition to other physiological and pathological activities. RBP4 is a low molecular weight protein and is labelled as the best indicator of tubular damage. RBP4 is also said to be an important marker of renal injury risks associated with macroalbuminuric diabetic nephropathy patients as compared to Scr measurement for early detection.[71]

3.20. Sodium/hydrogen exchanger isoform 3 (NHE3)

NHE3 is the most plentiful sodium transporter in tubules of kidney. A previous study has confirmed the presence of NHE3 in the urinary exosome of AKI patients.[72] Endogenous GLP-1R signalling exerts a physiologically relevant effect on the control of BP that might be

related to partly due to NHE3-mediated sodium reabsorption and its tonic actions on the proximal tubule, renin-angiotensin system, and insulin sensitivity.[73] As per the results of the immune system performed a semi-adjuvant on a fraction of the urinary membrane and diagnosed NHE-3 as a measurable marker in evaluating the difference between normal patients, patients with prenatal azotaemia, patients with acute glomerulus, and patients with ischemic/nephrotoxic acute tubular necrosis.[74,75] It can also predict AKI in neonates.[76]

3.21. Dickkopf-3

Dickkopf-3 is identified during stress-induced renal tubular cell- secreted glycoprotein which acts as a modulator during the investigations of the role of Wnt/β-catenin signalling in the promotion of AKI conversion to CKD signalling. Dickkopf-3 is expressed while renal tubular cell injury is still clinically inapparent; genetic abrogation of dickkopf-3 in vivo prevents tubule interstitial fibrosis and kidney disease progression in mice, potentially making dickkopf-3 a good marker of CKD progression. Stefan Schunk and colleagues, reported that urinary dickkopf-3 concentrations might reflect ongoing, previously undetectable tubular stress conveying high AKI risk, and improve AKI prediction beyond established clinical prediction models or available biomarkers. Use of dickkopf-3 as a marker might represent progress towards a personalised medicine approach to patients having effective surgery without other indication of AKI risk.[77]

3.22. Hepatocyte growth factor (HGF)

It has been reported in preclinical studies that HGF modification prevents worsening of the effects of human umbilical cord mesenchymal stem cells on rat AKI. It is considered to be a biomarker for an early acute renal failure.[78,79]

3.23. Trefoil factor 3

This factor is reported to be present as biomarker for gentamicin- induced toxicity and helps Predicts CKD in atherosclerotic communities.[80,70]

3.24. Glutathione S transferase (GST)

It is reported biomarker for AKI with paediatric intensive care unit.[81]

3.25. Proenkephalin (PENK)

PENK is a biomarker for sepsis -induced kidney injury, paediatric AKI, glomerular filtration rate and AKI.[82,83]

4. CONCLUSION

This review gives the direction to significant and promising biomarkers for acute kidney injury like neutrophil gelatinase-associated lipocalin, cystatin C, kidney injury molecule-1, monocyte chemotactic peptide-1, N-acetyl-β-D-glucosaminidase, interleukin-18, liver-type fatty acid-binding protein, netrin-1, cycle arrest markers like tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor–binding protein 7 (IGFBP7), endogenous ouabain, monocyte chemotactic peptide (MCP-1), Netrin-1,selenium-binding protein 1,BPIFA2 and some novel biomarkers like Sema 3A, suPAR, Retinol binding protein and kininogen 1, Sodium/hydrogen exchanger isoform 3 and dickkopf-3. Decline level of [TIMP-2] ·[IGFBP7] is the strongest predictor for renal recovery. Analysis of Interleukin-6 in AKI patients with SARS-CoV2 can predict AKI earlier. Further research will be more useful for future directions. Attempts to identify biomarkers to aid in early detection have led to the identification of a number of urinary and serum markers, and studies have shown that urinary markers are a priority because, at the time of admission, they can independently show the development of AKI earlier than serum creatinine; therefore, the use of these markers allows rapid diagnosis and quantification. Biomarkers have the potential to change the way patients with AKI are diagnosed and treated.

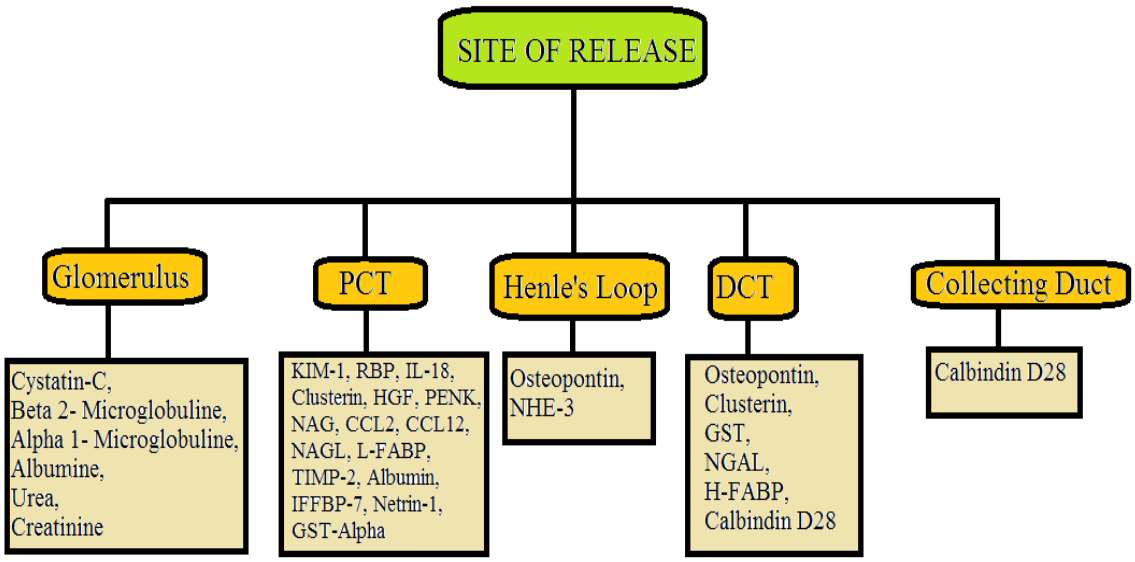

Fig. 1: Site of release for AKI biomarkers.[84]

Tables: Table 1 Biomarkers with their indications.

No.	AKI Biomarkers	Indications
1	TIMP-2. IGFBP-7	IGFBP7 ([TIMP-2] × [IGFBP7]), known as cell cycle arrest biomarkers, to aid critical care physicians and nephrologists in the early prediction of acute kidney injury in the critical care setting. This is an important marker for establishing cardiac surgery-related AKI.
2	NGAL	NGAL release 24 to 48 hours earlier than serum creatinine in patient at risk of AKI, for the detection of renal tubular toxicity, in burn and trauma related AKI. Biomarker for tacrolimus induced toxicity in liver transplant patient, for the prediction of AKI in patients with cardiac surgery, kidney transplant and critical illness. It is a biomarker for gentamicin induced toxicity.
3	Cystatin C	Cystatin C is a cysteine-protease inhibitor (molecular weight 13.3 kD) that is freely filtered but is degraded and/or resorbed in the renal tubule so that none appears in the urine. Since 1985, cystatin C has been suggested as marker of the renal function, provides early prediction of renal dysfunction in acute-on-chronic liver failure patients with a normal serum Cr level, prediction of AKI in patients with cardiac surgery, advanced liver diseases, and patients undergoing liver transplantation, for the assessment of renal function in patients with cirrhosis. In children with chronic kidney disease, CysC is a more accurate marker of glomerular filtration rate, with AKI release earlier than serum creatinine and also early prediction of AKI with COVID-19 patients.
4	KIM-1	Early indicators for cisplatin -induced AKI, can be detected in the urine of patients with (acute tubular necrosis. KIM-1 is expected to be a therapeutic target for kidney injury. It's a biomarker for various forms of nephrotoxic injury, cardiac surgery-induced kidney injury, transplant rejection, and chronic kidney diseases.
5	MCP-1	Higher plasma MCP-1 is reveals increased AKI and chances of mortality after heart surgery. Urinary epidermal growth factor (uEGF)/MCP-1 had a better ability to predict the composite endpoint and correlated more closely with kidney function decline in advanced diabetic kidney disease when compared with uEGF/Cr or uMCP-1/Cr alone.
6	NAG	NAG can be an important marker for assessment of nephrotoxicity of aminoglycosides and cephalosporins. It is recognised as an important marker for understanding changes of AKI and timely need for renal replacement therapy. Urinary NAG/Cr are significant biomarkers than serum Cr in earlier diagnosis and treatment of AKI in paediatric cancer patients.
7	Alpha1-microglobulin	Alpha1-microglobulin helps in detection of AKI in HIV patients.
8	IL-18	IL-18 can predict acute kidney disease in CVD patients. This biomarker has the highest sensitivity and specificity for early AKI diagnosis in intensive care unit.
9	L-FABP	Urinary L-FABP is recognised to be a sensitive biomarker of AKI in patients having abdominal aortic repair procedure.
10	Netrin-1	Netrin-1is a biomarker for AKI in post liver transplant patients. It might help in protection of proteinuria-induced renal injury.

11	EO	EO helps in AKI of critically ill patient and in cardiomyopathy- induced decreased renal function of patients. So, it can prove as valuable biomarker for heart failure.
12	SBP-1	SBP-1helps in chemical- induced nephrotoxicity, to detect early stages of kidney injury.
13	IL-6	Can be used for the detection of AKI in patients with COVID-19.
14	BPIFA-2	It plays role in sepsis induced AKI, in acute tubular necrosis, renal failure post-cardiac surgery, hepatorenal syndrome, and contrast nephropathy.
15	Micro RNA	miR-494 is a regulator of the renal inflammatory response as well as apoptosis after acute renal injury. miR-15b and miR-30a used as novel non-invasive biomarkers for gentamicin-induced acute kidney injury, Plasma levels of this microRNA could predict patient survival 4 weeks after initiation of renal replacement therapy.
16	LSS	LSS rs2254524 missense variant has been found strongly associated with an increased susceptibility of developing AKI following cardiac surgery.
17	Semaphorine 3A	It has an unknown role in the course of hexavalent chromium-Cr (VI)-induced nephrotoxicity. It's a mammalian target of the rapamycin (mTOR) pathway in renal injury or renal diseases.
18	suPAR	suPAR could represent a new category of AKI biomarker that is increased prior to AKI, predicts increased risk of AKI and has a pathogenic role in the development of AKI.
19	RBP	Biomarker for rentamicin -induced toxicity. Sensitive biomarker for loss of function of the human proximal renal tubule and for Renal fanconi syndrome.
20	NHE-3	NHE-3 is reported biomarker of AKI in neonates.
21	Dickkopf-3	It is involved in stress- induced renal tubular injury, for CKD progression, and AKI prediction after cardiac surgery.
22	HGF	HGF is biomarker for an early acute renal failure.
23	Trefoil factor-3	Trefoil factor-3 is a biomarker for gentamicin induced toxicity.
24	GST	GST is a biomarker for AKI with paediatric intensive care unit.
25	PENK	PENK is a biomarker for sepsis -induced kidney injury, paediatric AKI, GFR and AKI.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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