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Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges

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Abstract
Acute kidney injury (AKI) is strongly associated with increased morbidity and mortality in critically ill patients. Efforts to change its clinical course have failed because clinically available therapeutic measures are currently lacking, and early detection is impossible with serum creatinine (SCr). The demand for earlier markers has prompted the discovery of several candidates to serve this purpose. In this paper, we review available biomarker studies on the early predictive performance in developing AKI in adult critically ill patients. We make an effort to present the results from the perspective of possible clinical utility.

Keywords: AKI; biomarkers; ICU

Introduction

Acute kidney injury (AKI) represents an acute decline in renal function that leads to structural changes. AKI is associated with increased mortality, length of hospital stay and costs [1]. This unfavourable outcome might be tied to the late detection of AKI when the elevation of serum creatinine (SCr) is used. Many genes are up-regulated in the damaged kidney with the corresponding protein products appearing in plasma and urine. Some of these are candidate markers for more timely diagnosis of AKI. The purpose of this paper is to review the current state of epidemiological data concerning AKI, to evaluate available biomarkers for the prediction of AKI and to describe several potential therapeutic options.

Epidemiology of AKI in critically ill patients

The Beginning and Ending supportive therapy for the Kidney investigators study (BEST Kidney study) has provided recent global insight as to the prevalence of patients with AKI. The reported mortality rate is 60.3%, with sepsis and pre-morbid renal dysfunction being dominant causes. In this observation, 13.8% of the patients with acute renal failure (ARF) surviving until hospital discharge required chronic renal replacement therapy (RRT) [2]. AKI and AKI requiring RRT display increasing incidence due to the rising degree of comorbid conditions, increasing age and severity of illness in critically ill patients [3]. However, there seems to be a steady-state decline in annual in-hospital mortality (from 41.3% in 1988 to 28.1% in 2002). Despite the observed reduction in mortality rates, the rising incidence of AKI comes at a price. Patients tend to survive the intensive care unit (ICU) but will be discharged with various degrees of chronic kidney disease (CKD), which will increasingly strain the health care system [4]. These data are supported by observations from Australia, where the 10-year trend in the incidence of AKI and the crude hospital mortality rates adjusted for illness severity were likewise investigated. In this study, 5.2% of the patients have AKI with an increased incidence over the past decade; however, the multivariate adjusted odds of death associated with AKI show a declining trend. The increased risk of death associated with AKI persisted with the adjustment for several relevant covariates. ARF exerts an independent, profound and specific effect on morbidity and mortality in critically ill patients [5]. Furthermore, outcomes are directly related to the severity of AKI: even small changes in SCr have a detrimental impact on patient long-term survival [1, 6].

Biomarkers for the prediction of AKI

The ability of biomarkers to predict AKI has been studied intensely in several different clinical settings. For a sound interpretation of the reported results, it is important to realize that the studies present a mixture of ‘AKI diagnosis confirmation’ in patients with established AKI and ‘AKI early prediction’ in patients with developing AKI. Obviously, these are two different entities with different clinical impacts. For the clinical application of a new biomarker, it should prove to be more accurate with earlier detectability than the current gold standard SCr, which implies ‘early prediction’ only. Therefore, this review focuses on the prediction of developing AKI in adult critically ill patients. There are four major categories of biomarkers (Table 1).

Table 1. Biomarkers for AKI

Biomarker types	Biomarkers
Functional markers	SCr and plasma/serum CyC
Up-regulated proteins	NGAL, KIM-1, L-FABP and IL-18
Low-molecular weight proteins	Urine CyC
Enzymes	NAG, α-GST, π-GST, GGT and AP

Functional markers

Serum creatinine (SCr). Serum creatinine (SCr) is a degradation product of muscle cells and represents a surrogate for the efficiency of glomerular filtration. It has poor predictive accuracy for renal injury, particularly, in the early stages of AKI [7]. In the case of critical illness, SCr concentrations are subject to large fluctuations due to a patient's induced dilutional volume status, the catabolic effects of critical illness, the likelihood of concentration decreases in septic conditions and the increased tubular excretion with diminishing renal function. Furthermore, after an injurious event, the rise in SCr is slow. Therefore, detection of the earliest evidence of AKI necessitates the use of other plasma or urinary biomarkers.

Plasma/serum cystatin C (CyC). Cystatin C (CyC) is a 13-kDa non-glycosylated cysteine protease inhibitor produced by all nucleated cells at a constant rate. In healthy subjects, plasma CyC (pCyC) is excreted through glomerular filtration and metabolized completely by the proximal tubules. Furthermore, there is no evident tubular secretion. Several studies claim the superiority of pCyC against SCr to detect minor reductions in glomerular filtration rate (GFR) [8]. However, the interpretation of pCyC levels is biased by older age, gender, weight, height, cigarette smoking and high levels of C-reactive protein (CRP) [9, 10]. In addition, CyC levels are supposedly influenced by abnormal thyroid function [11, 12], the use of immunosuppressive therapy [13] and malignancies [14, 15]. In 318 patients included at ICU admission, pCyC predicted developing sustained AKI ($n = 19$) very modestly {area under the curve [AUC] = 0.65 [95% confidence interval (CI) 0.58–0.71]} in univariate analysis [16]. Herget-Rosenthal [17] described a cohort in whom sCyC was measured at admission in 85 patients with normal GFR. The reported AUC was 0.82 (CI 0.71–0.92) for acute renal failure 2 days prior to the event. A recent multicentre study in 151 subjects in a comparative setting found a poorer performance (AUC = 0.72 no CI provided) [18]. Metzger *et al.* [19] compared the classification performance of a set of urinary proteome analyses with sCyC in 20 general ICU patients, retrospectively, and found low classification accuracy (AUC = 0.67 CI not provided).

In cardio pulmonary bypass (CPB) cohorts, several studies explored the use of CyC for AKI prediction. Haase-Fielitz *et al.* [20] described 100 cardiac surgical patients among whom 23 subjects were classified as patients without preoperative renal impairment. Their samples were measured at ICU arrival, and the reported AUC = 0.78 (CI 0.58–0.99) did not improve after 24 h. Koyner *et al.* reported on 72 patients who were admitted following CPB with 34 subjects developing AKI, which was defined as a 25% increase in pCr or the need for RRT ($n = 7$) within 3 days after surgery. PCyC measured at the time of ICU arrival was not a useful early predictor for the composite outcome AUC = 0.62 (0.49–0.75) [21]. A likely explanation is the applied unusual definition of AKI, which indicates less severe grades of AKI among the event group.

Up-regulated proteins

Neutrophil gelatinase-associated lipocalin. Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein linked to neutrophil gelatinase in specific leukocyte granules [22]. It is also expressed in a variety of epithelial tissues associated with anti-microbial defence [23–26]. In the normal kidney, only the distal tubules and collecting ducts stain for NGAL expression. NGAL's composite molecule binds ferric siderophores, and furthermore, it is a potent epithelial growth inducer, has protective effects in ischaemia [27, 28] and is up-regulated by systemic bacterial infections [24, 29–32]. In the case of AKI, proximal tubule cells also stain for NGAL proteins, which is explained by megalin–cubilin-mediated re-uptake of NGAL present in the glomerular filtrate [33, 34]. Urinary NGAL originates from local production in the distal tubules and collecting ducts. However, uNGAL excretion is proportional to albumin excretion in mouse models of diabetic nephropathy and is thus augmented when the proximal transport maximum is exceeded [33, 35, 36]. Siew *et al.* [37] enrolled their patients within 24 h after admission and reported a receiver operating characteristic curve (ROC) AUC = 0.77 (CI 0.64–0.90) for developing AKI in a subgroup of patients with estimated glomerular filtration rate (eGFR) at admission >75 mL/min/1.73 m^2 for urine NGAL ($n = 18$ versus 257). Cruz *et al.* reported on the development of AKI within 48 h after first sampling an AUC = 0.78 (CI 0.65–0.90). However, the reported positive predictive value was low (24%), and within 5 days, the AUC was reduced to 0.67 (CI 0.55–0.79) [38]. The first sampling was performed within 24 h after ICU admission. De Geus *et al.* [39] came to roughly similar reports with samples at ICU admission in patients with eGFR >60 mL/min/1.73 m^2 for both plasma and uNGAL {AUC = 0.75 ± [standard error (SE)] 0.103} AUC NGAL = 0.79 ± (SE) 0.085. It is debatable whether the exclusion of patients with eGFR's <75 or 60 mL/min/1.73 m^2 applied by Siew and de Geus *et al.* is useful in clinical practice because a biomarker should also be effective in patients with CKD. In patients with sepsis, the predictive performance for AKI seemed not to be affected, as reported by Martensson for both plasma and urine NGAL [respectively, AUCs = 0.85 (CI 0.67–1.0) and 0.86 (CI 0.68–1.0)] [40]. However, Bagshaw *et al.* [41] report a distinct influence on test characteristics in patients with sepsis. Several studies report results in CPB cohorts: Koyner *et al.* [21] measured both pNGAL AUC 0.526 (0.388–0.664) and uNGAL AUC = 0.705 (CI 0.581–0.829) at ICU admission. An additional analysis by the same authors stratified their patients according to attained RIFLE stage and reported increased performances when using the harder end point of failure AUC = 0.69 (0.57–0.80) and AKIN Stage 3 AUC = 0.79 (0.65–0.94) [42]. A large study ($n = 426$) in CPB patients demonstrated test performance association with the pre-surgery baseline eGFR. Interestingly, only in patients with an eGFR above 60 mL/min was NGAL predictive: AUC = 0.68 (CI 0.54–0.81) [43]. A much smaller study ($n = 9$ events) reported values for both pNGAL and uNGAL, corrected for urinary creatinine: AUC = 0.85 (CI 0.73–0.97) and AUC = 0.96 (CI 0.90–1.0), respectively [44]. Haase-Fielitz [20] compared the performance of conventional and novel markers for pNGAL in adult CPB patients, excluding patients with preoperative renal impairment NGAL: the results yielded AUC = 0.80 (CI 0.58–0.99). In another large study ($n = 879$) for pNGAL measured immediately after CPB with 75 events, the AUC reported was 0.641 (0.58–0.71) [45]. Wagener *et al.* performed a study in adult CPB patients: for urine NGAL,

the predictive performance was AUC = 0.573 (CI 0.506–0.640) directly after the operation and the performance increased until 18 h after ICU admission to a maximum of 0.611. In a study performed by Liangos *et al.* [46], these results were similar in 103 CPB patients 2 h after surgery: AUC = 0.50 (CI 0.33–0.68) [47]. Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission, and the predictive performance for NGAL corrected for urinary creatinine concentration yielded AUC = 0.55 (CI 0.48–0.63) [48]. Metzger *et al.* compared the classification performance of urinary proteome analysis with classical markers. For urine NGAL, the ROC analysis revealed low classification accuracy: AUC = 0.54 CI (not provided) [19]. The only meta-analysis published to date assessed pNGAL's ability to predict across different settings; when weighted for study sample size, this value yielded an overall AUC of 0.782 (CI 0.689–0.872) [49].

Kidney injury molecule-1. Kidney injury molecule-1 (KIM-1) is a Type I transmembrane glycoprotein with a cleavable ectodomain (90 kDa) which is localized in the apical membrane of dilated tubules in acute and chronic injury [50, 51]. Kim-1 is believed to play a role in regeneration processes after epithelial injury and in the removal of dead cells in the tubular lumen through phagocytosis [50, 52]. A reduction in proteinuria with renine angiotensin aldosteron blockade is accompanied by a reduction in urinary KIM-1 excretion [53, 54]. Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission, and the predictive performance for KIM-1 corrected for urinary creatinine concentration yielded AUC = 0.55 (CI 0.47–0.62) in the study of Endre *et al.* [48]. Metzger *et al.* compared the classification performance of urinary proteome analysis with classical markers. For urine KIM-1, the ROC analysis revealed low classification accuracy (AUC = 0.71 CI, not provided) [19]. Several studies report its diagnostic properties in adult CPB patients [42, 47, 55–57]. Liang *et al.* reported an AUC for progressive AKI of 0.69 (CI 0.61–0.78) after 6 h of inclusion. Notably, adding KIM-1 to interleukin (IL)-18 [AUC for IL-18 for progressive AKI 6 h after inclusion was 0.87 (CI 0.80–0.93)] in a predictive model improved the model's accuracy only minimally [AUC 0.88 (CI 0.82–0.93)]. Liangos *et al.* reported an AUC 2-h post-CPB surgery of 0.78 (CI 0.64–0.91): however, in multivariate regression analysis, the association of KIM-1 was attenuated after adjustment. Koyner *et al.* [42] found an AUC 0.56 (CI 0.45–0.67) as admission value for the entire cohort with an improvement when predicting AKIN Stage 3 only [AUC = 0.69 (CI 0.44–0.93)].

Liver fatty acid binding protein. Fatty acid binding proteins are small (15 kDa) cytoplasmatic proteins abundantly expressed in tissues with active fatty acid metabolism. Their primary function is the facilitation of long-chain fatty acid transport, the regulation of gene expression and the reduction of oxidative stress. Urinary liver fatty acid binding protein (L-FABP) is undetectable in healthy control urine, which is explained by efficient proximal tubular internalization via megalin-mediated endocytosis [58, 59]. Under ischaemic conditions, tubular L-FABP gene expression is induced; in renal disease, the proximal tubular re-absorption of L-FABP is reduced [59, 60]. To date, there is one small study reporting on the early diagnostic performance of L-FABP in adult ICU patients. The reported ROC AUC value was 0.95, no CI provided. However, several uncertainties remain after disclosure of the study's methodology. Firstly, patient selection ($n = 25$ with 14 AKI and 11 non-AKI) seems to have been a result of convenient sampling. Secondly, the 'true early diagnosis' remains very doubtful as peak SCr and L-FABP values are reported as having the same median value; no further clear information concerning timing is provided [61].

Interleukin-18. In animal models, IL-18 has proven to be an important mediator in the process of AKI. Therefore, its urinary release has been anticipated as a possible early marker: several studies have explored the clinical application of this hypothesis.

Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission, and the predictive performance for IL-18 corrected for urinary creatinine concentration was AUC = 0.55 (CI 0.47–0.62) [48]. Metzger *et al.* compared the classification performance of urinary proteome analysis with classical markers. For urine IL-18, the ROC analysis revealed low classification accuracy (AUC = 0.57 CI not provided) [19]. Nevertheless, in a large cohort of mixed patients ($n = 451$), Siew *et al.* enrolled patients within 24 h after ICU admission: 86 developed AKI. The overall predictive performance reported was AUC = 0.62 (CI 0.54–0.69); this value increased slightly in patients with an eGFR above 75 mL/min/1.73 m^2 [AUC = 0.67 (CI 0.53–0.81)]. There seemed to be a strong association with sepsis [62]. In patients with acute lung injury, uIL-18 predicted progression to AKI within 24 h with an accuracy of AUC = 0.731 (CI not provided) with substantial overlap between cases and controls in urine concentrations [63]. In CPB patients, 2 hr after CPB time, the optimal performance was reported to yield an AUC = 0.66 (CI 0.49–0.83) [47].

Low-molecular weight proteins

Urine cystatin C. The urinary excretion of CyC (uCyC) specifically reflects tubular damage because systemically produced cystatin C is normally not found in urine [64]. However, recent insights show that urinary CyC excretion is augmented by albuminuria [65]. In patients without AKI on ICU entry, uCyC was not predictive of AKI occurring within 48 h with AUC = 0.54 (CI 0.46–0.62) [66]. Liangos *et al.* [47] used uCyC for this prediction, which resulted in very moderate performances 2-h post-CPB surgery with ROC AUC = 0.50 (CI 0.27–0.72) in a cohort of 103 patients with 13 events of AKI. In a study in patients undergoing CPB, Koyner *et al.* demonstrated that uCyC measured at ICU admission reached a maximum performance with an AUC of 0.693 (CI 0.567–0.818) [21, 48]. Among general adult ICU patients, 82 subjects developed AKI within 48 h of admission and the predictive performance for urine CyC corrected for urinary creatinine concentration yielded AUC = 0.55 (CI 0.48–0.63). Another study performed by Koyner *et al.* demonstrated the predictive value of uCyC at ICU admission for any stage of AKI with AUC = 0.72 (CI 0.61–0.83). For the prediction of AKIN Stage 3 versus the rest of the cohort, the predictive performance increased to AUC = 0.84 (CI 0.68–0.99) [42]. Royakkers *et al.* [18] regarded uCyC as a predictor for AKI 2 days prior to the first day of AKI and found no diagnostic value (AUC = 0.49 no CI provided).

Tubular enzymes

Alpha-glutathione s-transferase and pi-glutathione s-transferase. Alpha-glutathione s-transferase (α-GST) and pi-glutathione s-transferase (π-GST) are both members of a multigene family of detoxification enzymes present in

many organs including the kidney. Distribution across the entire nephron of structurally and functionally distinct isoforms has been demonstrated. In urine, these enzymes are normally not present. After injury, α-GST is primarily detected in the proximal cells, whereas π-GST is observed in the distal parts [67]. Westhuyzen *et al.* studied the predictive performance of tubular enzymes and their combination in adult critically ill patients. Four patients developed AKI defined as a 50% SCr increase or more. At the time of ICU admission, α-GST and π-GST measured and indexed to urine creatinine provided AUC's of 0.893 (CI 0.688–0.975) and 0.929 (0.740–0.990), respectively, [68]. However, the patients with AKI seemed to have established AKI at study inclusion with a median creatinine clearance of 38.1 mL/min. Walshe *et al.* reported that in patients with developing AKI and sepsis admitted to the general ICU, both enzymes were bad predictors. They suggested that sepsis might be the confounder triggering the production of these enzymes [69]. Finally, a study by Koyner *et al.* in 123 adult CPB patients reported AUC = 0.59 (CI 0.47–0.71) and 0.54 (0.42–0.66) for the prediction of AKI Stage 1 for α-GST and π-GST measured at ICU unadjusted for urine creatinine arrival, respectively, with similar test performances when using the harder end point of AKIN Stage 3 AUC = 0.58 (0.31–0.85) and AUC = 0.70 (0.50–0.90) [42].

Gammaglutanyl transpeptidase and alkaline phosphatase. Gammaglutanyl transpeptidase (GGT) and alkaline phosphatase (AP) both are tubular brush border enzymes that are released into urine when there has been significant damage to the brush border membrane with loss of the microvillus structures. Few clinical studies are available, but Westhuyzen *et al.* [68] report data on four cases with developing AKI respectively of AUC = 0.950 (CI 0.789–0.999) and AUC = 0.863 (CI 0.676–0.973). However, these results should be interpreted with caution because the cases must be considered as established AKI at study inclusion according to their reported creatinine clearance. In general adult ICU patients, 82 subjects developed AKI within 48 h of admission and the predictive performance for urine GGT and urine AP corrected for urinary creatinine concentration AUC = 0.57 (CI 0.50–0.64) and AUC 0.56 (CI 0.49–0.63), respectively [48].

N-acetyl-β-D-glucosaminidase. *N*-acetyl-β-D-glucosaminidase (NAG) is a lysosomal enzyme (>130 kDa) that is localized in the renal tubules. Due to its large molecular weight, it precludes glomerular filtration, implying that urinary elevations have a tubular origin. Increased activity suggests injury to its cells but may also reflect increased lysosomal activity without cell disruption. NAG catalyses the hydrolysis of terminal glucose residues in glycoproteins.

Westhuyzen [68] reported on the ability to predict developing AKI in four cases in general ICU patients with AUC = 0.845 (CI 0.639–0.955): however, these patients seem to have established AKI with reduced creatinine clearance at the time of study inclusion. In adult CPB patients, 13 cases of developing AKI were reported: and the 2-hr post-operative prediction for NAG was very moderate: AUC = 0.62 (CI 0.41–0.83) [47] (See Table 3 for a summary of all cited studies).

Treatment of AKI

The pathogenesis of AKI is very complex with multiple mechanisms underlying its course. Furthermore, critically ill patients do not generally die from AKI as such but more from the multiple organ dysfunction syndrome (MODS) associated with it. Given the multiple interactive pathways underlying AKI, it might be a mistake to concentrate therapeutic effects on one single part of the interrelated cascades. Therapies may need to target multiple sites in the pathophysiological pathways of AKI and MODS in order to be of any benefit for patients. Such combination therapies must involve agents with potential beneficial effects on vascular tone, tubular obstruction and inflammation. Furthermore, it is unlikely that targeting events that occur late in AKI will be effective. Pharmacological therapy in the prevention and treatment of AKI has been largely unsuccessful despite proven benefits as seen in pre-clinical studies. A number of drugs and investigational compounds seem promising in pre-clinical studies. There are six major categories of treatment strategies: anti-inflammatory agents, anti-apoptotic agents, iron scavengers, anti-oxidants, vasodilators and growth factors (Table 2).

Conclusions

In the quest for earlier markers for the recognition of AKI, several biomarkers have been investigated. The reported AUCs are disappointing ranging from 0.50 to 0.84, with one or two exceptions, which can be explained by statistical or methodological differences in study design. The discriminatory function in heterogeneous populations is poor and influenced by pre-existing renal function and time of sample collection with respect to the renal insult [48]. Clinical appraisal of a patient using standard parameters such as SCr and diuresis remains the cornerstone for now [70]. Therefore, it seems reasonable to perhaps shift our views and using biomarkers together with other parameters such as traditional clinical characteristics to optimize the accuracy of prediction of developing AKI might be an interesting option. Ultimately, the potential of new therapeutic agents can be tested and their use evaluated.

Table 2. Therapeutic agents for the treatment of AKI

Therapeutic agents category	Agents
Anti-inflammatory agents	β1 Integrin antagonist, adenosine receptor antagonist, mesenchymal stem cells, C5a receptor antagonist, IL-10, IL-6 antagonist, statins, erythropoietin, α melanocyte stimulating hormone, haeme oxygenase-1 inducers (rapamycin), activated protein C, toll like receptor (TLR) blockers (Eritoran), sphingosine 2A agonist, fibrates, statins, peroxisome proliferator activared receptor (PPAR)-γ agonist, minocycline, inducable nitric oxide (iNOS) inhibitor, insulin, ethyl pyruvate, C5-antagonists, alkaline phosphatase
Anti-apoptotic agents	NGAL, adenosine receptor antagonist, mesenchymal stem cells, erythropoietin, α-melanocyte stimulating hormone, caspase inhibitors, minocycline, guanosine, pifithrin-α, poly ADP ribose polymerase (PARP) inhibitor
Iron scavengers	NGAL, apotransferrin, deferoxamine
Reactive oxygen species scavengers	
Anti-oxidants	Edavarone, stobadine, deferoxamine
Vasodilators	Endothelin receptor antagonist, CO-releasing compounds, fenoldopam, anti natriuretic peptide
Growth factors	Erytropoetin, hepatocyte growth factor

Table 3. Summary of studies reporting predictive performance on biomarkers for developing AKI in adult critically ill patients[a]

Biomarker	Study (reference)	AUC (95% CI)	End point	Patient population
Plasma CyC	Nejat [16]	0.65 (0.58–0.71)	Sustained AKI	General ICU
	Herget-Rosenthal [17]	0.82 (0.71–0.92)	ARF	General ICU
	Haase-Fielitz [20]	0.75 (0.59–0.90)	AKI	CPB
	Koyner [21]	0.62 (0.49–0.75)	AKI[b]	CPB
	Metzger [19]	0.67 (-)	AKI	General ICU
	Haase-Fielitz [20]	0.78 (0.58–0.99)	AKI	CPB
	Royakkers [18]	0.62 (-)	AKI	General ICU
Plasma NGAL	Cruz [38]	0.78 (0.65–0.90)	AKI	General ICU
	De Geus [71]	0.75 (±SE 0.103)	RIFLE I and F	General ICU
	Martensson [40]	0.85 (0.67–1.0)	AKI	Septic general ICU
	Tuludhar [44]	0.85 (0.73–0.97)	AKI	CPB
	Haase [49]	0.782 (0.689–0.872)	AKI	Meta-analysis CPB and general ICU
	Haase-Fielitz [20]	0.80 (0.58–0.99)	AKI	CPB
	Perry [45]	0.641 (0.58–0.71)	AKI	CPB
Urine NGAL	Siew [37]	0.77 (0.64–0.90)	AKI	General ICU
	De Geus [39]	0.79 (±SE 0.085)	RIFLE I and F	General ICU
	Endre [48]	0.55 (0.48–0.63)	AKI	General ICU
	Liangos [47]	0.50 (CI 0.33–0.68)	AKI	CPB
	Koyner [21]	0.705 (0.581–0.829)	AKI	CPB
	Koyner [42]	0.69 (0.57–0.80)	AKI	CPB
	Koyner [42]	0.79 (0.65–0.94)	AKIN Stage 3	CPB
	McIlroy [43]	0.68 (0.54–0.81)	AKI	CPB
	Metzger [19]	0.54 (-)	AKI	General ICU
	Martensson [40]	0.86 (0.68–1.0)	AKI	Septic general ICU
	Tuladhar [44]	0.96 (0.90–1.0)	AKI	CPB
	Wagener [46]	0.573 (0.506–0.640)	AKI	CPB
Urine KIM-1	Liang [57]	0.69 (0.61–0.78)	AKI	CPB
	Liangos [47]	0.78 (0.64–0.91)	AKI	CPB
	Koyner [42]	0.56 (0.45–0.67)	AKI	CPB
	Koyner [42]	0.69 (0.44–0.93)	AKIN Stage 3	CPB
	Endre [48]	0.55 (0.47–0.62)	AKI	General ICU
	Metzger [19]	0.71 (-)	AKI	General ICU
Urine L-FABP	Matsui [61]	0.95 (-)	AKI	General ICU
Urine CyC	Liangos [47]	0.50 (0.27–0.72)	AKI	CPB
	Koyner [42]	0. 72 (0.61–0.83)	AKI	CPB
	Koyner [42]	0. 84 (0.68–0.99)	AKIN Stage 3	CPB
	Koyner [21]	0.693 (CI 0.567–0.818)	AKI[b]	CPB
	Nejat [66]	0.54 (CI 0.46–0.62)	AKI	General ICU
	Endre [48]	0.57 (0.50–0.64)	AKI	General ICU
	Endre [72]	0.57 (0.50–0.64)	AKI	General ICU
	Royakkers [18]	0.49 (-)	AKI	General ICU
Urine IL-18	Endre [48]	0.55 (0.47–0.62)	AKI	General ICU
	Liangos [47]	0.66 (0.49–0.83)	AKI	CPB
	Metzger [19]	0.57 (-)	AKI	General ICU
	Siew [62]	0.62 (CI 0.54–0.69)	AKI	General ICU
	Parikh [63]	0.731 (-)	AKI	ALI
Urine α-GST	Walshe [69]	–	AKI	General ICU with sepsis
	Koyner [42]	0.59 (0.47–0.71)	AKI	CPB
	Koyner [42]	0.58 (0.31–0.85)	AKIN Stage 3	CPB
	Westhuyzen [68]	0.893 (0.688–0.975)	AKI	General ICU
Urine π-GST	Koyner [42]	0.54 (0.42–0.66)	AKI	CPB
	Koyner [42]	0.70 (0.50–0.90)	AKIN Stage 3	CPB
	Westhuyzen [68]	0.929 (0.740–0.990)	AKI	General ICU
Urine NAG	Liangos [47]	0.62 (0.41–0.83)	AKI	CPB
	Westhuyzen [68]	0.845 (0.639–0.955)	AKI	General ICU
Urine GGT	Westhuyzen [68]	0.95 (CI 0.789–0.999)	AKI	General ICU
	Endre [48]	0.57 (CI 0.50–0.64)	AKI	General ICU
Urine AP	Westhuyzen [68]	0.863 (0.676–0.973)	AKI	General ICU
	Endre [48]	0.56 (0.49–0.63)	AKI	General ICU

[a](-), CI not provided and ALI, acute lung injury.
[b]study using different definition of AKI (SCr increase >25%).

Conflict of interest statement. None declared.

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