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# BIOMARKERS OF ACUTE KIDNEY INJURY IN A MIXED ICU POPULATION. A NARRATIVE REVIEW

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## Abstract

**Introduction:** Acute kidney injury is a severe complication occurring in critically ill patients treated in the intensive care units, which has a significant impact on morbidity and mortality in these patients. Moreover, despite technological and pharmaceutical advances during the last decades, acute kidney injury is still associated with markedly increased morbidity and mortality. Creatinine, the most common renal dysfunction biomarker in use, has poor predictive accuracy for renal injury due to time delay in its increase and the influence by other factors on its serum concentration such as age, gender, muscle mass etc. Therefore, the need for better renal biomarkers in order to early detect and intervene for acute kidney injury prevention is imperative. During the last years several new acute kidney injury biomarkers have been discovered and validated to improve early detection of patients in risk groups for progressive renal failure, need for renal replacement therapy or death.

**Aim:** The purpose of the present article is to review the studies that have tested the predictive ability of those biomarkers (in urine and/or plasma) for early detection of acute kidney injury in the mixed adult intensive care unit population.

**Material and Method:** We searched Medline (PubMed) using the keywords: acute kidney injury, biomarkers, renal failure, ICU.

**Results:** The most relevant articles were included in this review.

**Conclusions**: During the past decade, multiple AKI biomarkers have been studied and viewed as promising. Further studies are needed to determine their clinical utility.

**Key words: :** Acute kidney injury, biomarkers, renal failure, ICU.

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## INTRODUCTION

Acute kidney injury (AKI) consists of a rapid renal function decline or loss which usually increases serum urea and serum creatinine (sCr) levels, and induces uremic symptoms secondary to the accumulation of nitrogenous waste substances in the blood. AKI incidence varies from 1-7% of all hospitalized patients to 30-50% of intensive care unit (ICU) patients with 13,5% of them requiring renal replacement therapy (RRT). Despite many efforts to improve prevention and treatment, AKI is still associated with markedly increased morbidity, mortality and health care costs [1]. Because of the above-exposed reasons, AKI early identification is crucial for its prompt treatment and a better prognosis. The purpose of the present article is to review the studies that have tested the prognostic ability of all novel renal biomarkers for early AKI development in a mixed population of adult critically ill patients during the past decade (excluding cardiac surgery patients).

## DIAGNOSIS OF AKI

According to Kidney Disease Improving Global Outcomes (KDIGO) classification in 2012, AKI is diagnosed if sCr increases by 0,3mg/dl (26,5μmol/L) or more in 48h or rises to at least 1.5-fold from baseline within 7 days. AKI stages are defined by the maximum change of either sCr or urine output (UO) (UO<5ml/kg/h x 6-12h, or UO< 3ml/kg/h x 24h or anuria x 12h) [2]. As a result of recent standardization of diagnostic and staging criteria for AKI, our understanding of the epidemiology of AKI has improved in a variety of settings, including outpatient clinics, emergency departments, patient wards and ICUs.

### Creatinine limitations

sCr is a metabolite of creatine, a molecule that is synthesized from the amino acids glycine and arginine in liver, pancreas, and kidneys and that serves as a rapidly mobilizable reserve of high energy phosphates in skeletal muscles. Due to its low molecular weight (113 Da), creatinine is freely filtered by the glomeruli. In health, there is a constant production rate matching the rate of renal excretion [3].

The role of creatinine as a marker of renal function is limited by the fact that its half life increases from 4h to 24-72h if the glo-merular filtration rate (GFR) decreases. Thus, the serum concentration may take 24-36h to rise after a definite effect in renal function. Furthermore, a true fall in GFR may not be adequately reflected by sCr in patients with sepsis, liver disease and /or muscle wasting. Drugs also affect sCr concentration, which compete with tubular secretion. In this case, sCr may fluctuate without change in renal function [3-4].

Due to the fact that sCr is measured as a concentration, it is therefore affected by variation in volume status. As a result, the diagnosis of AKI may be delayed or missed in significant fluid shifts or fluid overload. A post-hoc analysis of the fluid and catheter management trial revealed that AKI was classified differently in up to 18% of patients after sCr was adjusted for net fluid balance and estimated total body water. Affected patients had mortality rates similar to those with AKI that was present before the adjustment [4].

In patients with normal kidney function, a rise in sCr by 0.3 mg/dl may be due to an important reduction in GFR. On the contrary, in patients with underlying CKD, rises in sCr represent variable changes in GFR and a rise by 0.3 mg/dl may be within the acceptable daily variation and reflect an inconsequential change in GFR.

Finally, single sCr values do not provide any information about specific stages of the AKI process. The most significant issue is that they do not indicate whether a patient is in a progression phase or if recovery has already begun. Also eGFR formulas are not valid to determine renal function in AKI [5].

### Urine output limitations

Oliguria is one of the oldest ''biomarkers'' of renal injury. Its association with AKI appeared more than 200 years ago as described by the English physician Heberden. However, the utility of oliguria as a predictor of AKI in hospitalized patients is limited by its relative sensitivity but poor specificity [6]. In fact, urine output may persist until renal function almost ceases. Therefore, the presence of oliguria may be misleading in that it may reflect a normal physiological response or may be indicative of transient haemodynamic disturbance and not necessarily indicative of significant tubular injury. Indeed, severe tubular injury may not be apparent initially as oliguria given that con-

centrating ability is disturbed. Under such circumstances, urine flow reflects GFR and oliguria will not be apparent until GFR has fallen significantly [7]. The KDIGO criteria for AKI are based on the presence of oliguria for a minimum 6h [2]. Several experts used a longer minimum period of oliguria (e.g. 12h) in order to provide a significant prediction of the development of AKI [8]. Others have found a correlation between the volume of urinary output and the duration of oliguria and recommended a lower threshold for urinary output (e.g. 0.3 ml/ kg/h instead of 0.5 ml/kg/h) for the definition of stage of AKI [9].

Given the increased risk for mortality associated with AKI, it is easy to understand why those patients who fulfill both urine output and sCr criteria for higher AKI stages do worse, suggesting renal impairment coupled with significant fall in GFR [9].

### AKI BIOMARKERS

A biomarker is defined as a structural, biochemical, physiologic or genetic parameter change, which indicates the presence, severity, or progress of a disease. Regarding kidney injury, it begins by inducing biological and molecular changes, which evolve to cellular damage and can be early detected by biomarkers, since they represent the early stress response of the kidney tubules injury [10].

The 10th Acute Dialysis Quality Initiative (ADQI) Consensus Conference suggested making use of both function and damage biomarkers in combination with traditional markers of renal function in order to define AKI [10]. The purpose was to transform the way clinicians diagnose and manage patients with AKI, by outlining its spectrum better than sCr and urine output alone. Several biomarkers of AKI in plasma or urine have been tested so far for their ability to predict AKI and need for RRT.

The availability of these new markers has allowed the detection of subtle changes in renal function before sCr rises and the identification of evidenced kidney injury, without a change in sCr (sub-clinical AKI) [11]. It is worth mentioning that biomarker positive, creatinine negative patients appear to have a greater risks of complications, longer hospital stay and higher mortality compared to patients without a biomarker rise. How-

ever in certain situations, these events reflect higher severity of illness rather than degree of AKI [10-11]. The main biomarkers are analyzed below.

### Neutrophil gelatinase - associated lipocalin (NGAL)

NGAL is a novel 25-KDa protein expressed by neutrophils and various epithelial cells. It is a member of the lipocalin family of proteins, which transport small hydrophobic molecules like steroids, retinoids, and lipids. NGAL concentrations are elevated in the serum of patients with acute bacterial infections, which is consistent with NGAL's proposed function as an endogenous bacteriostatic protein that scavenges bacterial siderophores (small molecules which bind iron). By binding iron, NGAL could mediate various physiologic functions, such as bacteriostatic and antioxidant effects. Additionally, there are data supporting a role of NGAL as a growth factor, regulating apoptosis or cell differentiation and as a regulator of the epithelial phenotype, inducing the formation of kidney epithelia in embryo and adults [12]. Mishra et al, initially proposed NGAL as an indicator for early renal injury secondary to renal hypoperfusion [13], and since then it has been studied in a variety of clinical contexts, both in children and adults. NGAL was found to be a useful early AKI predictor, operating its urine or serum levels equally well, having even prognostic value for initiation of dialysis and mortality. Comparing NGAL performance with sCr-derived glomerular filtration rate (eGFR), serum NGAL (sNGAL) and urine NGAL (uNGAL) had diagnostic superiority over sCr-based eGFR for predicting AKI. However, an increase in sNGAL generation does not seem specific to AKI, since it has been described in many pathologies such as chronic obstructive disease (COPD), severe pancreatitis, inflammatory bowel disease, chronic renal disease, as well as in ICU patients without AKI [12].

In a large prospective study of De Geus et al, 632 consecutive patients were included of whom 16% had AKI on entry. The percentage of patients with more severe AKI (RIFLE F) was 9%. The ROC-AUCs for AKI prediction 1 week after admission were 0.77 for admission plasma NGAL (pNGAL) and 0.80 for admission uNGAL, while the AUCs for RRT need were 0.88 for admission pNGAL and 0.89 for admission uNGAL [14]. In another

study which included 528 patients, Pickering et al aimed to evaluate the ability of pNGAL to reflect both decreased filtration and structural injury. On ICU entry the AUCs for the diagnosis of Functional AKI (defined by changes in sCr) was 0.74 and for Structural AKI (defined by elevations in uNGAL) was 0.79 respectively. pNGAL predicted the need for dialysis (AUC: 0.79), but not for death [15]. Hjortrup et al, in a prospective observational study concluded that in ICU patients with severe sepsis pNGAL and uNGAL had low predictive power for use of RRT, AKI and 90-day mortality. Two-hundred- twenty-two patients were included in the study. The AUCs for predicting use of RRT in ICU were 0.70 and 0.62 for pNGAL and uNGAL respectively. Moreover, the AUCs of pNGAL and uNGAL for AKI were 0.66 and 0.71, and for 90- day mortality 0.55 and 0.61, respectively. Combining NGAL values with sCr did not improve the AUCs [16]. Linko et al, in a prospective multi-centre study in 25 ICUs that included 369 patients, found that baseline pNGAL gives no additional value for prediction of hospital and 90-day mortality compared with severity scores (RIFLE or SAPS II) and has only moderate predictive power regarding RRT in critically ill adult patients with acute respiratory failure. The AUCs of baseline pNGAL were 0.73 for RRT, 0.62 for hospital and 0.58 for 90-day mortality, respectively [17], [Table 1].

**Cystatin C (CysC)**

CysC is a 13.3 kDa non-glycosylated cysteine protease inhibitor produced by all nucleated cells of the body, which is released into the intravascular compartment at a constant rate. CysC is freely filtered by the glomerulus, and subsequently reabsorbed by the renal proximal tubule through the endocytic receptor megalin and catabolized [12]. Unlike sCr, CysC is not secreted into the urine by the tubule, and it is not normally found in urine in significant amounts, although urinary CysC (uCys) excretion is increased by albuminuria. Consequently, serum cystatine (sCysC) concentration is a marker of glomerular filtration rate (GFR), whereas urinary CysC (uCysC) can reflect tubular damage [18]. The blood concentration of CysC depends on the individual's GFR, and the correlation between CysC and GFR is evident even in a range where sCr cannot detect changes, namely GFR of 60-90 mL/min; that means that sCr is insensitive

for small decreases in GFR. In more severe renal impairment accompanied by a marked reduction of the GFR, CysC could not demonstrate any superiority over sCr. It is important to recognize that the analysis of CysC may be affected by thyroid dysfunction, cigarette smoking, inflammation, cancer, and glucocorticoids but seems to be independent of gender, race, muscle mass, and hydration status [12, 18].

Nejat et al studied 444 critically ill patients. Based on the criteria used by the AKIN definition, 28% of patients had AKI on entry, 16% developed AKI over the subsequent 7 days, and 55% did not. Plasma CysC (pCyC) rose prior to sCr in 66% of patients developing AKI after entry. pCyC on entry was predictive for sustained AKI (AUC:0.80), defined as an increase in sCr of at least 50% from baseline for 24h or longer, but not for AKI within 7 days (AUC:0.65) [19]. In a multicenter prospective study, Royakkers et al studied 151 ICU patients that were separated in three groups: Group 0 (N=60): non -AKI, group 1 (N=35): AKI after admission, and group 2 (N=56): AKI at admission. They compared the two days prior to developing AKI from group 1 with the first two study days from group 0. The diagnostic performance for both pCysC (AUC: 0.72) and uCyC (AUC<0.50) was moderate 2 days prior to AKI diagnosis. Moreover, their prognostic ability for the need of RRT was poor (AUC $\leq$ 0.66) [20]. In another prospective observational study, Pipili et al tested the diagnostic performance of a panel of novel biomarkers in mechanically ventilated critically ill patients. sCyC and sCr showed early maximum predictive ability within 10 days of ICU admission. sCyC combined with either normalized uNGAL or absolute uNGAL were best predictors for RRT initiation (AUC-ROC: 0.8) [21], [Table 2].

**Kidney injury molecule -1 (KIM-1)**

Kidney injury molecule-1 (KIM-1) is a type I cell membrane glycoprotein containing a unique six cysteine immunoglobulin-like domains and a mucin domain in its extracellular portion. KIM-1 is expressed at low levels in the normal kidney and also in other organs, but its expression is significantly upregulated in the kidney after kidney injury, as it was initially identified using representational difference analysis on kidneys, following ischemia/reperfusion injury. In preclinical and clinical studies,

urinary KIM-1 (uKIM-1) has been used as an early diagnostic indicator of kidney injury. Studies in adults suggested that uKIM-1 was significantly elevated in patients with clinical diagnosis of acute tubular necrosis, and predicted adverse clinical outcomes, including dialysis requirement and mortality [22].

In a large prospective study of 529 patients, Endre et al, found that the AUCs of uKIM-1 for AKI prediction within 48 h post-admission, dialysis, and death prediction in 7 days, were 0.55, 0.62, and 0.56, correspondingly [23]. Analyzing data from the same population, Nejat et al found that uKIM-1 levels were significantly increased in pre-renal AKI compared with patients with no-AKI [24]. Furthermore, Koyner et al also described a predictive preoperative power of KIM-1 in relation to the development of stage 1 and stage 3 AKI. The preoperative KIM-1 was significantly different in those who did and did not go on to develop stage 1 AKI; KIM-1 provided an AUC of 0.67, whereas the KIM-1 early max performed even better (AUC: 0.69). KIM-1 was also useful for stage 3 AKI diagnosis with an AUC of 0.82 [25], [Table 3].

### Interleukin-18 (IL-18)

Interleukin-18, also known as interferon-gamma inducing factor, is a member of the IL-1 family of cytokines which regulates adaptive immunity. As an inactive 23-kDa percursor is synthesized by several tissues including monocytes, macrophages, and proximal tubular epithelial cells, and is processed into an active 18,3 kDa cytokine by a caspase-1. IL-18 levels are enhanced in numerous endogenous inflammatory processes, such as sepsis, inflammatory arthritis, inflammatory bowel diseases, systemic lupus erythematosus, psoriasis, hepatitis and multiple sclerosis, with this property significantly limiting its application due to low sensitivity and specificity. It is a sensitive mediator of ischemic injury in different organs (heart, brain, and kidney) [26]. IL-18 rises about 6h after the injury and peaks approximately 12h later at values up to 25 times of normal levels. During ischemic AKI, caspase-1 mediates conversion of pro-IL-18 to active IL-18, which is released from the tubular cell and mediates neutrophil infiltration into the renal parenchyma; thus IL-18 plays a deleterious role in AKI [12].

Endre et al, evaluated IL-18 among other biomarkers (NGAL, CysC, KIM-1, GGT, AP) in a prospective observational study of 523 ICU patients. The AUCs of uIL-18 for AKI diagnosis on entry and AKI prediction within 48h post-admission (in patients without AKI on entry) were 0.62 and 0.55 respectively. uIL-18 predicted dialysis and death with an AUC of 0.73 and 0.68, correspondingly. Performance was improved by stratification for eGFR or time or both. With eGFR<60 ml/min between 12 and 36h of injury, uIL-18 had utility (AUC:0.94) [23]. According to Doi et al, the AUCs of uIL-18 for AKI prediction within 1 week after admission and prediction of death 14 days post-entry were 0.69 and 0.83, respectively [27]. In another study by Doi et al, uIL-18 in patients with pre-renal AKI showed modest but significantly higher concentrations that in patients with non-AKI [28]. Finally, in a cohort study by Nisula et al, uIL-18 had poor to moderate ability to predict AKI (AUC: 0.58-0.66), RRT initiation (AUC: 0.65) and 90-day mortality in critically ill patients [29], [Table 4].

### Liver-type fatty acid- binding protein (L-FABP)

L-FABP, also known as fatty acid-binding protein 1 (FABP-1), is a 14-kDa protein from the large superfamily of lipid-binding proteins. FABPs are small (15KDa) cytoplasmic proteins abundantly expressed in all tissues with active fatty acid metabolism. Two types of FABPs have been identified in the human kidney: L-FABP in the proximal tubule and heart-type FABP (H-FABP) in the distal tubule. L-FABP binds selectively to free fatty acids (FFA), accomplishes the cellular uptake of fatty acids from plasma and regulates intracellular FFA metabolism [30]. L-FABP plays an important role as a cellular antioxidant during oxidative stress, by maintaining low levels of FFAs in the cytoplasm of tubular cells through the facilitation of intracellular metabolism and excretion in urine. Urinary liver fatty acid-binding protein (uL-FABP) is undetectable in healthy individuals, but under ischemic conditions, the tubular L-FABP gene expression is induced and in nephropathy, proximal tubular reabsorption of L-FABP is reduced [12].

In a prospective clinical study by Doi et al, 145 septic shock patients who were diagnosed as AKI at the time of ICU admission (established AKI) were analyzed. uL-FABP levels were significantly higher in non-survivors than in survivors and a multi-

ple logistic regression analysis revealed that uL-FABP was significantly associated with mortality. ROC curve analysis revealed an AUC of 0.99 for death prediction [31]. Likewise, Doi et al found an AUC of 0.90 for 14-day mortality for uL-FABP measured on ICU admission. The AUC of uL-FABP for AKI prediction 1 week post- ICU entry was 0.75 [27]. Finally, findings from a recent study showed that high uL-FABP-1 and uL-FABP-3 levels could serve as markers for AKI patients with risk for dialysis need (p< 0.001) [32], [ Table 5].

## TIMP-2 and IGFBP7

Tissue inhibitor of metalloproteinases 2 (TIMP-2) is 21-kDa protein, member of the TIMP family. TIMP-2 is an endogenous inhibitor of metalloproteinase activities. Insulin- like growth factor-binding protein 7 (IGFBP-7), a 29- kDa secreted protein, is known to bind and inhibit signaling via insulin-like growth factor 1 receptors. Both markers are involved in the process of G1 cell-cycle arrest that prevents cells from dividing in case of damage to the DNA until such damage can be repaired. TIMP-2 and IGFBP-7 are markers of cellular stress in the early phase of tubular cell injury caused by a variety of insults (ischemia, oxidative stress, inflammation, drugs and toxins) [33].

[TIMP-2] X [IGFBP-7] was indicated as a fair to excellent biomarker, in the ICU setting, in predicting moderate to severe AKI. In a landmark two stage multicenter study Kashani et al, tested the ability of 340 proteins, including known AKI biomarkers, to predict development of AKI in an ICU population. TIMP-2 and IGFBP7 were validated in the second study-phase (Sapphire). In the final analysis cohort (heterogeneous sample of 728 critically ill patients) the two biomarkers were significantly superior in order to forecast AKI stage 2 or 3. They demonstrated an AUC of 0.80 [34]. Furthermore, follow up studies using a cutoff value of 0.3 ng/ml for urinary [TIMP-2] X [IGFBP7], ascertained an AUC of 0.82 [35] and 0.79 [36] for the prediction of AKI stages 2 and 3 respectively. These findings indicated that, in the ICU setting [TIMP-2] X [IGFBP-7] is fair to excellent biomarker in predicting moderate to severe AKI within 12h (mainly among those who are categorized at high risk for AKI). In a long term follow-up study Koyner et al, showed that urinary [TIMP-2] X [IGFBP7] levels greater than 3.0 ng/ml

were associated with death or RRT requirement during the next 9 months in patients who developed AKI, [37] [Table 6].

## Endogenous ouabain

Endogenous ouabain (EO) is a neuroendocrine hormone synthesized in the adrenal cortex. EO modulates the Na, K- ATPase pump activity and induces signal transduction via sodium-calcium exchange and the Src-dependent pathway. The hypertensive effect of EO is associated with organ damage and it is well established in both animal and human models. The mechanism of the EO effect is likely mediated by changes in cell $Ca^{++}$ (activation of the $Ca^{++}$-dependent protease calpain with an increase in nephrin protein cleavage or, via activation of the transcriptional regulator Snail with reduction in nephrin expression) [38].

In a study of Bignami et al, elevated preoperative EO levels were associated with a higher incidence of postoperative AKI (20.3 vs 2.8%, p<0.001) and ICU stay (2.4 +/- 0.59 vs. 1.4+/- 0.38 days, p=0.014) [39]. In another study of Simonini et al, the preoperative EO value was added to a different clinical AKI predictive model and resulted in a significant improvement of risk prediction power (AUC of AKI from 0.79 to 0.84 ; p < 0.0001) [40],[Table 5].

## N-acetyl-β-glucosaminidase (NAG)

NAG is a lysosomal enzyme mainly found in the proximal tubule cells. Increased urinary concentration of NAG is a sensitive marker that may suggest renal injury. NAG enzyme is not filtrated by the glomerulus due to relatively high molecular weight (~ 140 kDa), but in active kidney disease urinary NAG (uNAG) levels are elevated. The utility of NAG still remains limited due to the fact that its urinary excretion is also elevated in chronic glomerular diseases [26].

Doi et al, reported that in critically ill patients uNAG was a moderate predictor of both AKI within 1 week after admission (AUC: 0.62) and 14-day mortality (AUC: 0.66) [27]. Moreover, another study by Doi et al, found that patients with pre-renal AKI had higher concentrations of uNAG than patients with non-AKI [28], [Table 5].

## CONCLUSIONS

AKI among critically ill patients is common worldwide and is associated with high morbidity, mortality, and prolonged hospitalization. Timely identification of AKI and appropriate implementation of preventive strategies are thought to be the most effective tools to improve AKI outcomes. During the past decade, multiple AKI biomarkers have been studied and viewed as promising, with the purpose of allowing clinicians to identify kidney injury earlier. So far, studies for NGAL have reported fair to moderate results for AKI prediction in the mixed ICU setting. [TIMP-2] X [IGFBP-] performed better in ICU patients that are categorized at high risk for AKI than any other reported biomarker to date. Moreover, it is strongly suggested that biomarkers be used in large randomized studies in order to validate the role of each one of them (or a panel of them) in order to determine their clinical utility for earlier AKI diagnosis and improved risk assessment.

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**ANNEX**

**TABLE 1.** Performance of NGAL in the mixed adult ICU. Studies with AUC-ROC analysis.

| Author (ref) year | Sample size | Baseline sCr estimation if unknown | AKI defini-tion | % AKI On entry | % Total AKI | AKI tim-ing | Sampling/ assay(s) | %AUC (95% CI) for AKI | %AUC (95% CI) for RRT | %AUC (95% CI) for death |
|---|---|---|---|---|---|---|---|---|---|---|
| **DeGeus[14] 2011** | 632 | Admission sCr | RIFLE | 16 | 27 | 7 days | Serum and urine/ Triage Biosite | 77(72-82)[s] 80 (76-84)[u] | 88(82-94)[s] 89(85-93)[u] | 63(57-69)[s] 64(58-70)[u] |
| **Pickering[15] 2013** | 528 | Lowest of the admis-sion or final ICU sCr | RIFLE | NA | 68 | 7 days | NGAL ELISA KIT[u] / Triage NGAL Test [s] | 74(69-79)[F] 79(74-83)[$] 79(75-83)[t] | 79(66-91)[t] | 58(50-67)[t] |
| **Hjortrup[16] 2014** | 222[†] | Pre-admission sCr/ MDRD equation | KDIGO | 41 | 24 | 2 days | The NGAL Test | 66(54-77)[s] 71(59-82)[u] | 70(61-78)[s] 62(51-73)[u] | 55(47-63)[s] 61(53-70)[u] |
| **Linko[17] 2013** | 369[†] | Admission sCr | RIFLE | NA | NA | 7 days | Triage NGAL test | NA | 73(65-81)[S] | 58(52-64)[s] |

┼: multicenter study; s: serum or plasma specimen, u: urine specimen; F: Functional-AKI = an increase in plasma creatinine or either > 26.4 μmol/l(0.3mg/dl) or >50%;.S: Structural AKI: urinary NGAL > 18.7 ng/ml(mmol/l creatinine); t: total performance

**TABLE 2**. Performance of CysC in the mixed adult ICU. Studies with AUC-ROC analysi

| Author (ref) year | Sam-ple size | Baseline sCr estima-tion if un-known | AKI defini-tion | % AKI On entry | % Total AKI | AKI timing | Sam-pling/ assay(s) | %AUC(95% CI) for AKI | %AUC (95% CI) for RRT | % AUC (95% CI) for death |
|---|---|---|---|---|---|---|---|---|---|---|
| **Nejat[19] 2010** | 444[†] | Lowest of the admis-sion or final ICU sCr | AKIN | 28 | 45 | 7 days | Serum/ Nephe-lometry | 78(73-83) [s,d] 65(58-71)[s,p] | 84(69-99)[p] | 62(53-72) |
| **Royak-kers[20] 2011** | 151[†] | MDRD equation | RIFLE | 37 | 60 | NA | Serum and urine / nephe-lometry | 72(NA)[s, *, P] 49(NA)[u,*,p] 50(NA)[u,*,p] | 66(NA)[s, b] 61(NA)[u, b] 60(NA)[u, b] | NA |
| **Pipili[21]** | 106 | sCr up to 6 months before ICU | RIFLE | 20 | 41 | 10 days | MNII nephe-lometer | NA | 76(NA) [s] | NA |

┼: multicenter study; **s**: serum or plasma specimen; u: urine specimen; d: diagnosis of established AKI on admission; p: prediction of newly diagnosed AKI after ICU admission, in patients without AKI on entry; b: on day of AKI diagnosis; *: 2 days prior to AKI diagnosis NA: not available or not applicable.

**TABLE 3.** Performance of KIM-1 in the mixed adult ICU. Studies with AUC-ROC analysi

| Author (ref.) year | Sample Size | Baseline sCr estimation if unknown | AKI defi-nition | % AKI On entry | % Total AKI | AKI timing | Sampling assay(s) | % AUC (95% CI) p for AKI | % AUC (95% CI) p for RRT | %AUC (95% CI) p for death |
|---|---|---|---|---|---|---|---|---|---|---|
| **Endre**[23] **2011** | 529[+] | Lowest on admission | AKIN | 27.8 | 48.4 | 7 days | Microsphere –based lu-minex XMAP | 66(61-72)[d] P<0.0001 55(47-62)[p] P=0.21 | 62(48-76) P: 0.1 | 56(47-64) P: 0.17 |
| **Nejat**[24] **2012** | 529[+] | Lowest on entry on ICU, Pre-surgery | AKIN | NA | 41.7 | 7 days | Microsphere-based lu-minex XMAP | P: 0.028[x] P<0.001[y] P<0.034[z] | NA | NA |
| **Koyner**[25] **2010** | 123 | Lowest on admission, Pre-operatively | AKIN 48 RIFLE 24 | NA | 37.4 | 5 days | Microsphere-based lu-minex XMAP | 67(57-77) (P=0.05)[I] 82(68-95) (P<0.05)[III] | NA | NA |

╁: multicenter study; d: diagnosis of established AKI on admission; p: prediction of newly diagnosed AKI after ICU admission, in pa-tients without AKI on entry; x: Pre-renal AKI vs no-AKI; y: AKI 48 vs no-AKI; z: AKI 48 vs pre-renal AKI; I: stage I AKI; III: STAGE III AKI; NA: not available or not applicable.

**TABLE 4.** Performance of IL-18 in the mixed adult ICU. Studies with AUC-ROC analysis

| AUTHOR (ref) Year | Sample size | Baseline sCr (estimation if un-known) | AKI definition | % AKI On entry | % Total AKI | AKI timing | Sampling/ assay(s) | %AUC (95% CI) For AKI | %AUC (95% CI) For RRT | %AUC (95%CI) For Death |
|---|---|---|---|---|---|---|---|---|---|---|
| **Endre**[23] **2011** | 529[+] | Lowest on admission | AKIN | 27.8 | 48.4 | 7 days | Urine/ELISA kit | 62(56-67)[d] 55(47-62)[p] | 73(59-86) | 68(60-76) |
| **Doi**[27] **2011** | 339 | Last value 3 months before ad-mission, MDRD Equation | RIFFLE | 19.2 | 39 | 7 days | Urine/ ELI-SA kit | 78(70-84)[d] 59(51-67)[p] 68(62-74)[t] | NA | 82(68-91) |
| **Nisula**[29] **2014** | 1439[+] | Latest value from the previous year, MDRD Equation | KDIGO | 46.1 | 34.5 | 3 days | Urine/ELISA kit | 58(54-62) | 65(57-74) | 53(49-57) |

╁: multicenter study; d: diagnosis of established AKI on admission; p: prediction of newly diagnosed AKI after ICU admission, in patients wit AKI on entry; t: total performance (d+p); NA: not available or not applicable.

**TABLE 5**. Performance of EO, NAG and L-FABP in the mixed adult ICU. Studies with AUC-ROC analysis.

| Author (ref) year | Sample size | Baseline sCr estimation if unknown | AKI definition | % AKI on entry | % total AKI | AKI timing | Sampling /assays | %AUC (95% CI) for AKI | %AUC (95% CI) for RRT | % AUC (95% CI) for death |
|---|---|---|---|---|---|---|---|---|---|---|
| EO Bignami[39] 2013 | 626 | 2 months before surgery | AKIN | NA | 10.3[x] | 5 days | Milan radio Immuno-assay | 75(69-81) P<0.0001 | P=0.014 | NA |
| Simonini[40] 2014 | 802 | 2 months before surgery | AKIN | | 9.9 | | NA | 79(73-84) P<0.0001 | NA | NA |
| NAG Doi[27] 2011 | 339 | MDRD equation | RIFLE | 19 | 39 | 7 days | Urine/ 4-HP-NAG substrate method | 70(62-76)[d] 55(47-62)[p] 62(56-68)[t] | NA | 66(50-80) |
| L-FABP Doi[27] 2011 | 339 | MDRD equation | RIFLE | 19 | 39 | 7 days | Urine/ ELISA kit | 80(73-86)[d] 70(62-76)[p] 75(69-80)[t] | NA | 90(83-94) |

x: stage II, III AKI; d: diagnosis of established AKI on admission; p: prediction of newly diagnosed AKI after ICU admission, in patients without AKI; t: total performance, NA: not available or not applicable.

**TABLE 6**. Performance of TIMP-2 X IGFBP-7 in the mixed adult ICU. Studies with AUC-ROC analysis.

| Author (ref.) year | Sample size | Baseline sCr estimation if unknown | AKI definition | % AKI On entry | % Total AKI | AKI timing | Sampling/assay(s) | %AUC (95% CI) for AKI[x] | %AUC (95% CI) for RRT | %AUC (95% CI) for death |
|---|---|---|---|---|---|---|---|---|---|---|
| Kashani[34] 2013 | 728[†] | 6 months to 6 days prior to enrollment | RIFLE/AKIN | NA | 43 (14[x)]) | 12h | Elisa/Luminex 200 MSD Sector Images 6000/ Astute140 Meter -Nephrocheck | 80(NA) | NA | NA |
| Bihorac[35] 2014 | 420[†] | 6 months before enrollment | KDIGO | NA | (17[x)]) | 12h | Astute 140 Meter -Nephrocheck | 82(76-88) | NA | NA |
| Hoste[36] 2014 | 154 | Median at least 5 sCr values 6 months prior to enrollment | KDIGO | NA | 39.9 (18[x)]) | 12h | Elisa/ Luminex 200 MSD Sector Images 6000/ Astute 140 Meter -Nephrocheck | 79(69-88) | NA | NA |

†: multicenter study; X: AKI stage 2 and 3; NA: not available or not applicable