Chapter 4
Diagnosis of AKI: Clinical Assessment, Novel Biomarkers, History, and Perspectives

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Abstract Around year 2005, vague definition of acute renal failure was replaced by diagnosis of AKI, which aimed to establish an internationally unified criteria detecting kidney damage earlier. During the following decade, novel urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL or lipocalin 2), liver-type fatty acid-binding protein (L-FABP or FABP1), kidney injury molecule-1 (KIM-1), and NephroCheck (product of urinary TIMP-2 and IGFBP7) emerged and were intensively investigated, which made it possible to detect kidney damage even earlier than development of AKI. These markers led to concepts of forest fire theory, functional/damage biomarkers, and subclinical AKI. By considering the time course and mechanism, we propose here that those urinary biomarkers may be divided into two categories: tubular dysfunction biomarkers (markers at least partially and potentially reflecting super-acute phase proximal tubule reabsorption impairment, which are urinary NGAL, L-FABP, and NephroCheck) and tubular regeneration biomarkers (early AKI markers but relatively delayed, reflecting proximal tubule regeneration, which contain urinary KIM-1). Future perspectives of novel AKI biomarkers include evaluation of biomarker-based early intervention and biomarker-guided AKI therapy using biomarkers to judge effectiveness of on-going treatments.

Keywords Urinary biomarkers · Emerging biomarkers · Forest fire theory
Functional/damage biomarkers · Subclinical AKI · NGAL · L-FABP · KIM-1
NephroCheck

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4.1 Historical Changes in the Concept of AKI

Correlation of blood creatinine levels with glomerular filtration rate (GFR) or creatinine clearance was first proposed in 1926 and was verified by succeeding works [1–4]. Since then till now, serum creatinine has been long the gold standard to define renal function or GFR in other words. Acute elevation in serum creatinine or blood urea nitrogen levels has been called acute renal failure. It was a vague concept, making it impossible to compare the findings of different clinical studies both horizontally and historically. As described above in this book, national consortiums began to propose internationally united criteria to define acute renal failure, especially in the early phase, and gave a term of acute kidney injury (AKI). Based upon changes in serum creatinine levels and urine outputs, RIFLE criteria by the Acute Dialysis Quality Initiative (ADQI) were published in 2004 [5] and AKI Network criteria in 2007 [6], and they were combined as 2012 AKI criteria by the Kidney Disease: Improving Global Outcomes (KDIGO) [7]. In KDIGO AKI criteria, the mildest stage of AKI (stage 1) was defined as either of the followings: (1) elevation of serum creatinine levels by $\geq$0.3 mg/dL within 48 h, (2) elevation of serum creatinine levels by $\geq$1.5-fold within 7 days, or (3) decrease of urine output to $\leq$0.5 mL/kg/h for more than 6 h [7]. We believe that, for healthy progress of nephrology, international definition of AKI should not be changed for at least 10 years. During years 1998–2013, novel urinary biomarkers representatively listed in Table 4.1 emerged, which are increased both in rodent and human AKI.

4.2 Which Were Earlier, Human Studies or Rodent Studies of Urinary AKI Biomarkers?

Sequences of urinary biomarker reports, in the settings of rodent and human AKI and human CKD, are clearly distinct among biomarkers (Table 4.1). In 2002, NGAL appeared in the nephrology literature for the first time, as one of kidney

Table 4.1 Representative urinary biomarkers for AKI and their first reports in rodent AKI, human AKI, and human CKD

Urinary biomarker	NGAL	L-FABP	KIM-1	NephroCheck
First in rodent AKI	Mishra et al. (2003) [11]	[a]Kamijo et al. (2004b) [19]	Ichimura et al. (2004) [16]	Peng et al. (2016) [22]
First in human AKI	Mori et al. (2005) [12] Mishra et al. (2005) [13]	Portilla et al. (2008) [20]	Han et al. (2002) [15]	Kashani et al. (2013) [21]
First in human CKD	Mori et al. (2005) [12]	Kamijo et al. (2004a) [18]	Timmeren et al. (2007) [17]	Not reported

[a]Indicates that the report dealt with unique transgenic mice harboring human L-FABP genetic locus, whose findings cannot be tested in standard laboratory animals

differentiation/epithelialization inducers [8, 9]. In 2003, upregulation of renal NGAL mRNA expression was reported at 3–24 h after murine renal ischemia-reperfusion injury [10]. Increase of NGAL protein in the urine was reported in murine renal ischemia-reperfusion injury and cisplatin-induced nephrotoxicity in 2003 [11]. Elevation of urinary NGAL levels in human AKI [12, 13] and human CKD [12] was reported in 2005.

In 1998, induction of renal KIM-1 mRNA expression was reported at 48 h after rat renal ischemia-reperfusion injury [14]. Increased excretion of urinary KIM-1 was reported in human AKI in 2002 [15], rat AKI in 2004 [16], and human CKD in 2007 [17].

On the other hand, elevation of urinary L-FABP was first reported in human CKD in 2004 [18], followed by AKI in genetically modified mice in 2004 [19] and human AKI in 2008 [20].

Increase of NephroCheck [product of urinary concentrations of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7)] was reported in human AKI in 2013 [21] and in rat AKI in 2016 [22]. NephroCheck in human CKD has not been reported. The sources of urinary TIMP-2 and IGFBP7 in AKI are poorly understood [23]. While IGFBP7 and TIMP-2 are speculated to be synthesized by injured renal tubules [21], there is no supporting evidence.

NGAL and KIM-1 have been the top two most popular biomarkers reported in the annual scientific meetings of the American Society of Nephrology (Fig. 4.1). The ratio of total abstract numbers may not necessarily reflect the numbers of large-scale clinical studies but might indicate reproducibility of the findings across various AKI etiologies in different countries.

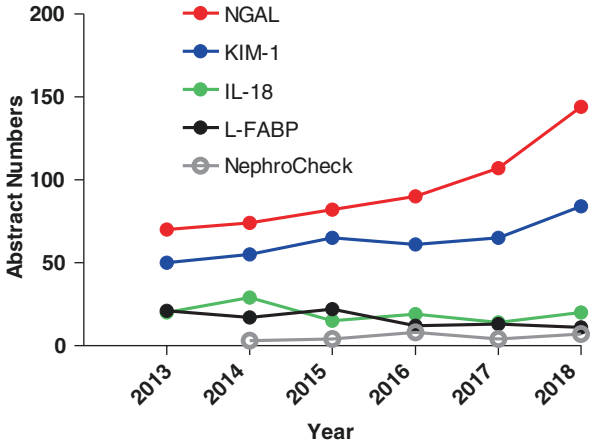

Fig. 4.1 Abstract numbers of five urinary AKI biomarkers in Kidney Week. Online abstracts of the American Society of Nephrology Kidney Week in the recent 6 years were searched using each biomarker name. To enhance screening, other key words such as lipocalin 2 and LCN2 for NGAL and TIMP-2 and IGFBP7 for NephroCheck were also used. The abstract numbers included studies in basic science not related to urinary biomarker levels but dealt with, for instance, biological function of the proteins or phenotypic analysis of knockout and transgenic mice. Of note, publication-only abstracts which were not selected for presentation in the meeting were also included

4.3 Prediction of AKI by Novel Biomarkers

Soon after discovery of those AKI biomarkers, it was recognized that those biomarkers commonly allow early prediction of AKI development (i.e., significant elevation of serum creatinine levels several days later) on the day of kidney insult (Fig. 4.2) [13, 20, 24, 25]. With the introduction of these biomarkers other than GFR indicators (serum creatinine, serum cystatin C, or creatinine clearance) or urine output, the field of AKI entered a new era.

Forest fire theory in 2007 (Fig. 4.3) proposed that blood, urine, and kidney NGAL concentrations are the real-time indicators of active kidney damage (resembling red fire in forest fire), distinctly from markers of functional nephron numbers such as serum creatinine or GFR (ratio between viable and burnt trees) [26].

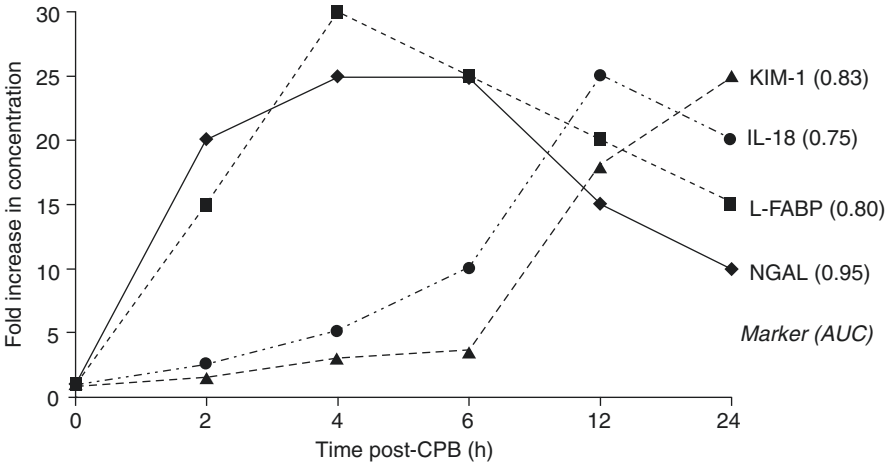

Fig. 4.2 Changes of urinary biomarkers in AKI cases after cardiopulmonary bypass surgery. *CPB* cardiopulmonary bypass, *AUC* area under the curve for the prediction of AKI. Reproduced from Devarajan (2010) [51]

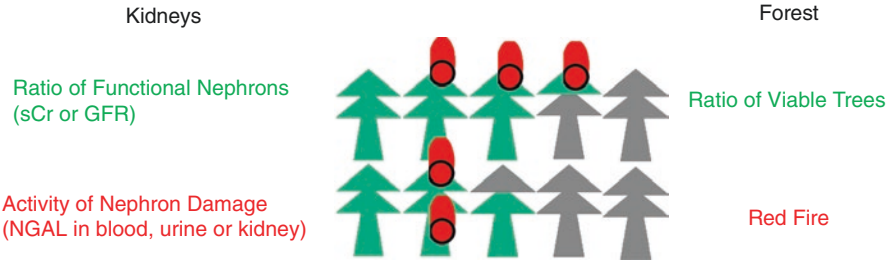

Fig. 4.3 Forest fire theory for worsening renal function. Reproduced from Mori and Nakao (2007) [26]. *sCr* serum creatinine, *GFR* glomerular filtration rate

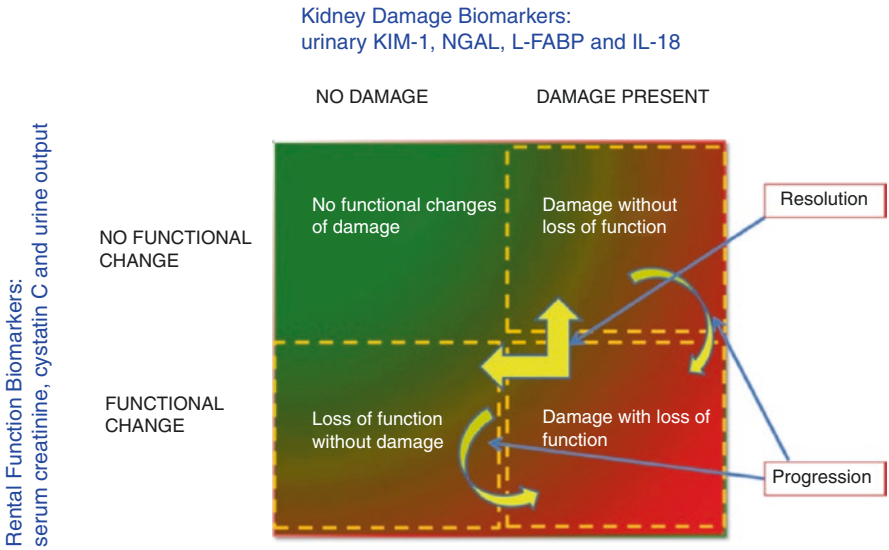

Fig. 4.4 Biomarker-based framework for AKI evaluation. Reproduced from Murray et al. (2014) [28]

In 2013–2014, ADQI 10th Workgroup reported a two-dimensional, biomarker-based framework for AKI evaluation (Fig. 4.4) [27, 28]. In that framework, serum creatinine, serum cystatin C, and urine output are renal function biomarkers, whereas urinary KIM-1, NGAL, L-FABP, and IL-18 are examples of kidney damage biomarkers. The lower left quadrant represents loss of function without damage which is often reversible. This scenario has been called dehydration, prerenal AKI, or transient AKI. The upper right quadrant indicates damage without loss of function, which was alternatively named subclinical AKI [29]. In subclinical AKI, loss of function may not develop at all or be seen at some time interval after detection of damage biomarkers. These patients are at higher risk for renal replacement therapy (RRT) requirement and mortality compared to patients without an increase in damage biomarker levels [29].

4.4 Clinical Use of Novel AKI Biomarkers

Some of the urinary biomarkers are locally available for clinical use [30, 31]: NGAL in Japan (since February 2017) and in Europe, L-FABP in Japan (since August 2011), and NephroCheck in the USA (since September 2014). Additionally, KIM-1 is approved by the Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) for preclinical drug development and clinical trials [32].

4.5 Novel Classification of AKI Biomarkers: Tubular Dysfunction Biomarkers and Tubular Regeneration Biomarkers

Cardiac surgery with cardiopulmonary bypass (CPB) is a unique situation with high AKI risk, in which the initiation of the renal insult (i.e., renal ischemia) can be clearly defined. It is well established that urinary levels of NGAL and L-FABP in patients who are going to develop AKI start to increase within a few hours after the start of CPB, and they begin to decrease within 6–12 h (Fig. 4.2) [13, 20, 33, 34]. Many literatures insist that de novo synthesis of NGAL occurs in response to AKI, based upon the findings in renal ischemia-reperfusion injury (RIR) of animal studies [12, 35]. However, those experimental settings are quite severe, and it seems unlikely that urinary NGAL levels start to decrease within 12 h in those animals. In rodent RIR, loss of polarity and dislocation of Na-K-ATPase in tubules is the first event, followed by cell death and dedifferentiation/regeneration of tubular cells [36]. Activity of Na-K-ATPase provides an essential force for endocytic reabsorption of proteins in the proximal tubule lumen [37]. Megalin expressed along the apical surface of proximal tubules is responsible of capturing and endocytosis of luminal proteins including NGAL and L-FABP [38, 39]. Transient and reversible dysfunction of proximal tubules as to endocytic capacity is a more reasonable explanation for rapid changes in urinary biomarkers after cardiac surgery, other than de novo mRNA transcription, protein synthesis, secretion from tubular cells, and replacement of dead tubular cells. Since molecular weights of TIMP-2 and IGFBP7 are similar to those of NGAL and L-FABP [23] and elevation of NephroCheck is as early as NGAL in human AKI [21], TIMP-2 and IGFBP7 may undergo similar renal metabolism as NGAL. On the other hand, elevation of urinary KIM-1 levels starts 12 h after CPB initiation [24], likely reflecting the dedifferentiation/regeneration phase [14]. Therefore, we propose here that urinary albumin, NGAL, L-FABP, and NephroCheck, at least partly and potentially, have features of tubular dysfunction biomarkers, while urinary KIM-1 is a tubular regeneration biomarker. Consistently, when a systematic review was carried out for AKI biomarkers in 2008, urine KIM-1 performed best for the differential diagnosis of established AKI, whereas urine NGAL and IL-18 performed best for early diagnosis of AKI [40].

4.6 Future Perspective

A recently published meta-analysis showed a clear and statistically significant mortality benefit to early nephrology consultation [41]. Indeed, in a cardiac surgery study, early detection of post-surgery kidney injury by increase in NephroCheck allowed early intervention by nephrologists and reduced incidence of AKI [42].

There are continued efforts to evaluate whether monitoring of AKI biomarkers, such as urinary NGAL, is useful to judge trend in the kidney injury severity and treatment efficacy in the setting of AKI or subacute CKD [43, 44]. In a dog model of gentamicin-induced AKI, increase and decrease of urinary NGAL levels were earlier than the change of serum creatinine by approximately 4 days [45] (Fig. 4.5a). In our case undergoing intermittent hemodialysis after severe post-infectious glomerulonephritis, serum creatinine levels were not good indicator of renal function due to removal by hemodialysis. Decrease in urinary NGAL levels was steeper than that of urinary L-FABP levels, which occurred 2 weeks earlier than dialysis withdrawal in this case (Fig. 4.5b).

Importantly, theoretical exercises have shown that even a perfect biomarker will perform poorly when compared to an imperfect gold standard [46–48]. In dehydrated conditions, serum creatinine levels increase and may fulfil criteria of AKI, but urinary NGAL is not sensitive to dehydration [49, 50]. In some forms of acute tubular necrosis, serum creatinine or GFR may not be altered significantly in the early phase, despite increase in urinary AKI biomarkers. Therefore, a race to develop and compare biomarkers which have the strongest power (the largest area under the curve in receiver operating characteristic curve analysis) for the prediction of creatinine and urine output-based AKI may not be very fruitful as expected.

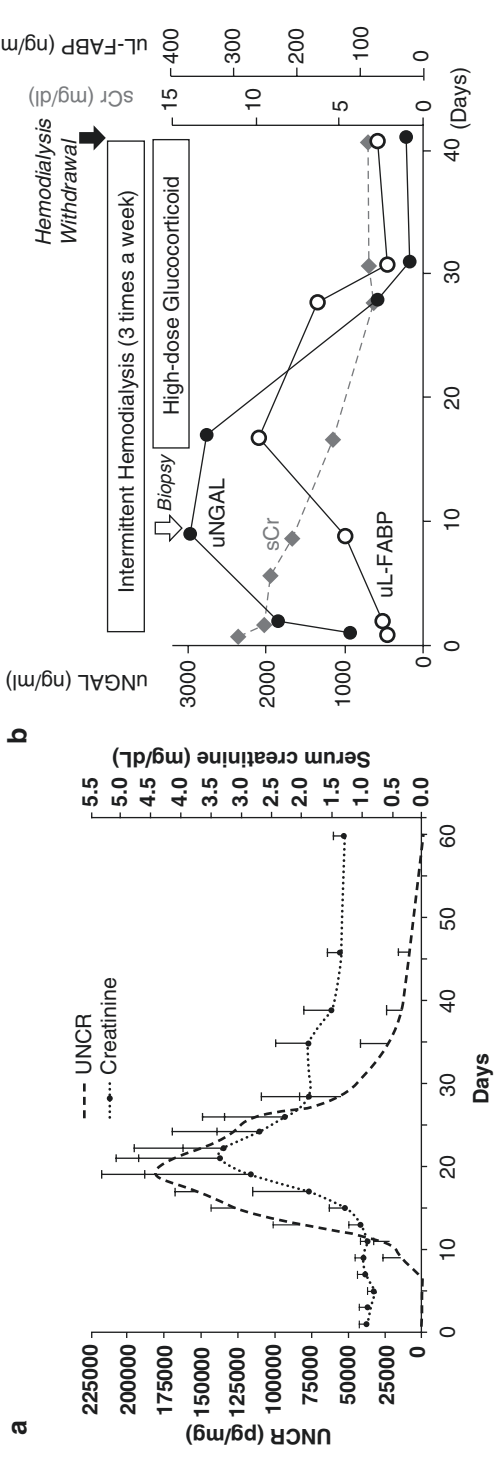

Fig. 4.5 Time course of urinary biomarkers during recovery phase of AKI. (**a**) Changes in serum creatinine and urinary NGAL/creatinine ratio (UNCR) in a dog model of gentamicin-induced AKI. Reproduced from Plam et al. (2016) [45]. (**b**) Changes in serum creatinine (sCr) and urinary NGAL (uNGAL) and L-FABP (uL-FABP) levels in a case with post-*Staphylococcus aureus* infection, acute glomerulonephritis treated with hemodialysis, and high-dose glucocorticoid. A case observed in Shizuoka General Hospital. White and black arrows indicate the timing of renal biopsy and hemodialysis withdrawal, respectively

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