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Acute Kidney Injury Biomarkers – from bench to clinical use

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INTRODUCTION

Acute kidney injury (AKI) is common and the absolute incidence of AKI has increased over the last decade[1]. Almost 10% of hospitalized patients can develop AKI; incidence is even greater in the intensive care unit (ICU) and emergency department (ED) settings, respectively attaining 30% and 20% in Portugal[2,3]. AKI is a complex syndrome that occurs in many different settings, resulting from different insults, with a wide variety of subtypes and with diverse aetiologies. AKI can manifest from small increases in serum creatinine (SCr) to the urgent need for renal replacement therapy (RRT). AKI has a well-documented negative impact on kidney and patient survival in the short- and long-term[1]. Serum creatinine is an imprecise and delayed marker of AKI. Extensive pre-clinical and clinical research on AKI biomarkers has opened up a new era in this field. It has been asserted that more timely diagnosis using novel AKI biomarkers would allow earlier intervention and could improve patient outcomes. Herein we aim to summarize the major studies that have characterized the diagnostic and prognostic predictive power of novel AKI biomarkers, together with our experience.

AKI BIOMARKERS: WHERE WE ARE

A biomarker is a measurable indicator of normal biological or pathological processes and/or the expression of response to some intervention. Novel AKI biomarkers have undoubtedly attained an important role in diagnosis, prognosis and even prediction, not just for AKI but also for associated outcomes, but only in specific research fields. The question of how to optimally use them at the bedside is still unresolved. Despite the large number and extent of biomarkers proposed over the last decade, our high expectations have not been followed by a reliable change in our clinical practice. Apparently, we have not found sufficient reasons to abandon SCr, despite its limitations.

We could benefit from early AKI diagnosis if we had a kidney-specific biomarker to avoid iatrogenic interventions, attenuate damage and enhance recovery. Earlier AKI diagnosis may identify patients with mild AKI that may not be recognized by clinicians. Given the current lack of effective pharmacologic interventions for AKI, early recognition should mainly address reducing the risk of injury progression. This risk assessment for AKI has been recommended by clinical practice guidelines[4].

The performance of AKI biomarkers is influenced by many factors: settings, population studied, time of measurement after insult, threshold diagnosis of AKI and study design, among others. All are closely related to the complexity of the pathogenesis and pathobiology of the AKI syndrome. This has been demonstrated by the lower test performance of six biomarkers in AKI patients with pre-existing CKD[5].

RELEVANT BIOMARKERS CURRENTLY USED IN RESEARCH

The biomarkers deemed most relevant in research in the last decade include functional biomarkers (SCr, and serum cystatin C (CysC)); markers of tubular damage such as tubular enzymes (γ-glutamyl transpeptidase (GGT), N-acetyl-β- glucosaminidase, α-glutathione-S transferase); non-absorbed tubular proteins (urinary CysC, albuminuria, β2-microglobulin and α1-microglobulin); or upregulated proteins induced by tubular injury (kidney injury molecule 1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL), interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP) and recently, cell cycle arrest proteins such as tissue inhibitor of metalloproteinase-2 (TIMP-2) and IGF-binding protein 7 (IGFBP7)).

Several previous studies were limited by reliance on a single measurement of biomarkers. Recent studies have revealed a distinct temporal profile for AKI biomarkers[6]. In the Emergency Department (ED) setting, the temporal profile of plasma NGAL (pNGAL) and serum CysC (SCysC) for AKI diagnosis showed peaks at 12h from admission and performance at that time was the best[2,3].

Owing to the broad range of published results and several in-depth reviews, we would conclude that the most relevant biomarkers with potential for use in clinical practice are those able to detect structural kidney damage, such as pNGAL and urinary NGAL (uNGAL), KIM-1, IL-18, L-FABP, and TIMP-2, and IGFBP7. Despite more than a decade of intensive research efforts, the role of those markers at the bedside for decision making remains unclear. However, SCysC performed better than SCr as a filtration marker and for risk stratification; IL-18 and uNGAL preceded SCr and were associated to AKI risk and adverse outcomes such as RRT and death, both improving the clinical prediction model[7,8]. The current status of the most promising AKI biomarkers is shown in Table 1.

The NGAL gene is primarily induced in the distal nephron; NGAL protein can be found in both the distal and the proximal nephron., NGAL protein found in the proximal nephron reflects megalin-dependent avid reabsorption of filtered NGAL by the proximal tubule. Therefore NGAL possesses many characteristics of a good AKI biomarker. It is rapidly induced and released from the injured distal nephron; pNGAl and uNGAL concentrations increase proportionally in line with the severity and duration of injury; and it rapidly decreases with attenuation of AKI[9]. pNGAL can detect patients with probable subclinical AKI who are at increased risk of adverse outcomes, in the absence of SCr changes[3,9]. Despite all these positive characteristics, both uNGAL and pNGAL have shown mixed results in a number of studies. Standardized clinical platforms for the routine clinical measurement of NGAL are now widely available. In a recent decision analysis model, the use of uNGAL was shown to represent an economically advantageous strategy for the early diagnosis of AKI in patients undergoing cardiac surgery[10].

In the ED setting, among 5 urinary biomarkers (NGAL, KIM-1, LFABP, IL-18 and CysC), uNGAL enables prospective diagnostic and prognostic stratification of AKI, as it is able to distinguish between preAKI, stable CKD and normal function[11]. We also have shown this discriminative ability of SCysC and pNGAL[2,3]. As markers of poor outcomes (RRT, CKD, and death), uNGAL and KIM-1 were the most accurate predictors.

TIMP-2 and IGFBP7 are cell-cycle arrest proteins expressed in kidney tubular cells during cellular stress or injury. By detecting both proteins in the urine, we detect cell stress at the earliest point. However, this stress may or may not lead to damage and dysfunction[13]. Both

Table 1

Main abilities of AKI biomarkers according to reviewed literature

Biomarker	Kidney specificity	Improving Diagnosis					Improving Prognosis			
		early	discriminative	grading severity	recovery	etiology	AKI progression	RRT	CKD	mortality
Serum Cystatin C		√		√			√		√	√
uNGAL/pNGAL		√	√	√	√		√	√	√	√
KIM-1	√		√	√	√		√	√	√	√
L-FABP		√		√			√	√		√
[TIMP-2]-[IGFBP7]	√	√		√	√		√	√		√

AKI, acute kidney injury; RRT. Renal replacement therapy; CKD, chronic kidney disease; NGAL, neutrophil gelatinase–associated lipocalin (uNGAL, urinary; pNGAL, plasma); KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid-binding protein; TIMP-2, tissue inhibitor of metalloproteinase-2; and IGFBP7, IGF-binding protein 7.

proteins are capable of inducing a wide variety of cellular response, whereby their presumed role as inducers of G1 cell cycle arrest remains speculative[14]. In discovery phase, 340 different proteins were examined; urinary IGFBP7 and TIMP-2 were the best-performing markers[15]. In a second multicentre study, SAPPHIRE, both markers were validated as being able to predict the onset of severe AKI (KDIGO stage 2 or 3) more accurately than uNGAL, KIM-1, IL-18, L-FABP or urinary cystatin C. [TIMP-2]-[IGFBP7] showed improved performance for risk stratification, risk of adverse events such as RRT, persistent kidney dysfunction and death. The multicentre TOPAZ study validated the high-sensitivity cutoff value of [TIMP-2]-[IGFBP7] for risk assessment of AKI, diagnosed by clinical adjudication in critically ill patients[16]. But high sensitivity (92%) was associated to low specificity (46%). Hence, false-positive results may be common and magnified if the test is used in low-risk patients.

A bedside device test was developed for simultaneous measurement of [TIMP-2]-[IGFBP7]: the NEPHROCHECK Test (ASTUTE140 Meter), which takes 20 minutes, performing only one test at a time. The Food and Drug Administration has approved it for AKI risk detection but its cost benefit is still unknown. More recently, several studies have shown the improved performance of this test in assessing the risk for AKI and predicting outcomes[17]. Nevertheless, the optimal role of this biomarker in different clinical settings requires further clarification. The ASN advisory group emphasizes that this test should only be used in ICU patients >21 years of age with cardiovascular and/or respiratory compromise within the previous 24h. It should therefore not be used for point-of-care testing.

MOVING FORWARD CLINICAL APPLICATIONS OF BIOMARKERS

For a biomarker to be transferred to our daily clinical practice, it is essential to consider the clinical setting, and also to plan which clinical intervention or care we must implement in response to a biomarker increase. We propose a stratification of the risk of AKI depending on pNGAL levels, identifying a high-risk zone encompassing patients who are likely to benefit from intensive monitoring and treatment; a moderate-risk or grey zone, for those who require re-evaluation or the addition of a different associated biomarker; and a low-risk zone, for those patients in whom surveillance can be safely reduced. We have shown that both SCysC and pNGAL rise before SCr, at 12h from study admission, and, therefore, these markers are able to predict the development of AKI and allow the institution of early goal-directed therapy (change doses of medication and increase haemodinamic support to improve haemodynamic status) aiming at AKI risk reduction. Moreover, these patients should be closely followed after discharge because they frequently develop CKD and End Stage Renal Disease[8]. In cases with increased SCr due to transient azotaemia, the absence of an increase in a structural AKI biomarker such as pNGAL would indicate a functional volume-responsive AKI, with an improved prognosis. A suggested approach for the use of pNGAL in the clinical setting is shown in Table 2.

Table 2

Proposed use of pNGAL in the clinical setting

Measure pNGAL only if AKI is clinically suspected	False positives may include urinary tract infections and sepsis without AKI
<50 ng/ml	Low risk of AKI, repeat measures only if clinically indicated
50-150 ng/ml	Grey zone, repeat measures
150-300 ng/ml	High risk for structural tubular injury, obtain daily pNGAL measurements, monitor ins and outs, monitor electrolytes and kidney function, avoid nephrotoxins, avoid hypotension, consider Nephrology consult
>300 ng/ml	High risk for severe structural tubular injury, obtain daily pNGAL measurements, keep in ICU setting, closely monitor ins and outs, closely monitor electrolytes and kidney function, avoid nephrotoxins, avoid hypotension, obtain Nephrology consult, strongly consider early interventions

But above all, we must include the clinical context in biomarker performance. Patient-dependent variables such as demographic characteristics and comorbidities should be taken into account to evaluate the risk of AKI and associated outcomes, as we have shown that age, kidney susceptibility and cardiovascular disease are critical in ED for AKI development, as well as for adverse outcomes such as CKD and death[8].

In recent years, electronic alert systems have been proposed for early detection of AKI using current definition criteria, with the goal of warning clinicians early and optimizing intervention. The Acute Dialysis Quality Initiative (ADQI) workgroup has encouraged development of this tool for early AKI detection[18].

AKI diagnosis based on SCr may represent a misdiagnosis more frequently than we have thought. We have shown that pNGAL can increase in the absence of a significant rise of SCr, and during the follow-up

time it could be associated to CKD evolution[8]. So should the current AKI definition based on SCr be changed?

There is no sense in using a biomarker for AKI diagnosis when the diagnosis is clinically evident and biochemically confirmed. In such cases, it is useful to utilize a biomarker to forecast or predict progression, RRT need or recovery.

Some studies have shown very impressive results and concur with the concept that AKI biomarkers have the potential to transform current AKI diagnosis criteria. Conversely, we still confront significant unresolved concerns that currently hamper efforts to bring biomarkers from the bench to the bedside.

■ DISCLOSURE

KS declared no competing interests. PD is a co-inventor of submitted patents on the use of NGAL as a biomarker of kidney injury.

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