In this issue of the journal, Wang et al. describe a novel approach for assessing risk for inpatient mortality using different definitions of acute kidney injury (AKI). The authors use absolute changes in serum creatinine (SCr) instead of changes in stages as defined by KDIGO AKI guidelines, and demonstrate that the net reclassification index (NRI) for mortality risk is almost 10%, and therefore likely useful in clinical practice. The findings require validation in an external dataset, but are certainly promising.

This paper and area of research is important on a number of counts. First, it heralds the commitment of the scientific community to generate research to get the definitions ‘right’ of common entities. The need to practically evaluate definitions within the context of clinical care cannot be overstated. These authors, as have others, pursue the need for precision and practical application of detecting AKI in hospitalized patients. Secondly, it confirms previous concepts that small changes in SCr confer risk, and that use of first hospital SCr as baseline SCr performs well in this context. Previous authors have worked out complex methods to ascertain ‘baseline SCr’, so the validation that a delta SCr within the same admission is of value in predicting outcomes will be a welcome simplification to previous propositions. The improved ability to predict important events is critical if we are to design clinical trials, and do so with appropriate sample size calculation.

Acute kidney injury remains an important event in patients with and without chronic kidney disease (CKD). Despite recent advances in understanding AKI pathophysiology including discovery of novel biomarkers, and in the role of renal replacement therapy in an AKI setting, AKI still affects more than 60% of patients depending of context and definitions, and is associated with in-hospital mortality reaching almost 60% for dialysis-requiring AKI in an intensive care unit (ICU) setting [1]. As a syndrome, caused by diverse etiologies, with variable severity, it requires consistent definition. Choosing an AKI definition necessarily influences estimates of AKI incidence or outcomes, and design of future research. Therefore, differences and implications for each potential AKI definition should be well evaluated. However, applying a single AKI definition across all studies and in all settings is impossible. For example, precise time frame for SCr measurements (e.g. 48 h) is easy to comply with in a randomized-controlled trial taking place in an ICU, but may be much more difficult to apply in a retrospective observational outpatient study where SCr measurements are not pre-specified.

Before 2004 when Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal disease (RIFLE) was proposed, more than 30 definitions were used in the literature [2, 3]. While RIFLE and subsequent definitions do have limitations, they were beneficial for the clinical and research communities, and have great strengths. As consistent attempts at quantifying the elements of acute kidney damage (changes in SCr and urine output), the definitions have proved useful. The development of the definitions was consensus-based, involving multidisciplinary experts from around the world. This led to uptake of those definitions due to wide acceptance, which greatly improved homogeneity and comparability of AKI studies.

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Secondly, they propagated the concept of AKI stages, using severity of damage and prognosis to differentiate the stages. Thirdly, they defined clear time frame periods for AKI diagnosis, which permitted an improved consistency between studies. Finally, although less often used, and not yet rigorously evaluated, the use of quantitative urine output criteria over fixed time periods, proposed as an alternative or supplement to SCr, focused attention on the other key important function of the kidney: solute and water excretion. Reduced urine output may occur in advance of changes in SCr, or even confound that measure. As recognized by RIFLE working group, urine output is not specific but it may change earlier than SCr [3]. However, urine output criteria are difficult to capture in administrative databases, and difficult to accurately quantify in non-critical care hospital settings or outpatient settings, and without intensive data collection in clinical studies.

In 2007, AKIN was proposed as a revised version of RIFLE [4]. In addition to proposing the term AKI instead of acute renal failure, two major changes proposed by AKIN compared with RIFLE were (i) the inclusion of a short time frame (48 h) to identify AKI and (ii) inclusion of small SCr changes (≥0.3 mg/dL) in addition to the previous 50% increase in SCr criterion. This later criterion was added based on increasing evidence that small changes in SCr were associated with increased mortality [5], a fact again confirmed by Wang et al. While numerous studies compared RIFLE and AKIN for mortality prediction (mostly in ICU or cardiac surgery settings), neither is clearly superior [2]. In 2012, the KDIGO working group proposed another AKI definition based on RIFLE and AKIN definitions, the reference definition used by Wang et al. [6]. Modifications in the KDIGO guideline from the AKIN proposal are mostly related to time frames for SCr measurements. While RIFLE and AKIN have been validated in various clinical settings, validation of the newly refined KDIGO definitions has not yet been undertaken.

As in many guidelines, several limitations of the recommendations were proposed by the working group, and research topics were suggested [6]. The need to determine the value of absolute versus relative changes of SCr at different time point was one such research recommendation. Thus, the work from Wang et al. is an excellent first step. Other recommendations not addressed by these authors were the evaluation of the influence of urine output criteria, comparing the use of SCr versus estimated glomerular filtration rate (eGFR), determining the role of novel biomarkers, and evaluating how to apply AKI definition in patients with lower levels of eGFR.

Before the publication of the RIFLE, AKIN and KDIGO definitions, one of the most used and validated AKI definition was from Hou et al. [7]. Interestingly, this early AKI definition was based on absolute changes in SCr (an increase of 0.5 mg/dL when baseline SCr is <2 mg/dL, or 1.0 mg/dL if baseline SCr is between 2.0 and 4.9 mg/dL, or 1.5 mg/dL if baseline SCr is above or equal to 5.0 mg/dL), instead of relative changes as actual definitions. This definition had the advantages of being simple and taking into account pre-existing levels of kidney impairment. While the debate between using absolute versus relative changes in SCr is not new, the current paper in this edition of the journal is an important, timely and useful addition to the paucity of literature on this topic.

Intuitively, relative changes in SCr makes more sense than absolute changes because of the inverse relation between SCr and creatinine clearance. As discussed by Waikar et al. [8], a 50% reduction to SCr clearance should lead to a 100% increase in SCr whatever is the baseline SCr. In the opposite, a 50% reduction in SCr clearance would lead to various absolute increases in SCr, depending on the baseline SCr. However, the problem with this theoretical relation is that steady state is not attained in clinically relevant time frames, where absolute changes may be more reliable, as demonstrated by Waikar et al. [8]. It should be remembered however that absolute increases in SCr may not be adequate for some patients with low baseline SCr (pregnant women, children, conditions with muscle wasting). It is not clear how this subgroup of patients is represented in the current Wang study, but given the likelihood that that group is very small and underrepresented, it would not influence the overall NRI. Similarly, this delta-creatinine method may not apply to severe CKD patients (where a small change in SCr may be an expected day-to-day variation). Again, for the same drop in renal function a higher increment in SCr would occur for a CKD patient than for a non-CKD patient. For this reason, an absolute increase of 0.4 mg/dL, for example, would carry a lesser mortality risk among severe CKD patients than non-CKD patients, which has been confirmed by at least two recent studies [9, 10]. This study did not find any subgroup differences among those with CKD, so that finding should be interpreted with caution, given that the phenomena occurs more frequently at eGFR below <30 mL/min/1.73 m², and may be missed at eGFR levels between 30 and 60 mL/min/1.73m² [9, 10]. When using absolute increase in SCr among CKD patients, timing of SCr measurement is important as shown by Waikar et al. [8].

A limitation to the Wang paper is that the improved NRI may not only be explained by using absolute versus relative changes in SCr, but by defining different thresholds for the three AKI stages. Of note, AKIN and related KDIGO definitions also included absolute changes in SCr, but only for stage 1 AKI. For example, a patient with a normal baseline SCr of 0.9 mg/dL and reaching 1.2 mg/dL (a 0.3 mg/dL) would be classified as stage 1 AKI (and therefore AKI in general) using both AKIN and delta-creatinine methods. However, the same patient would need to reach 2.7 mg/dL with the KDIGO definition to be classified as stage 3 AKI instead of 2.1 mg/dL with the delta-creatinine proposed method. It remains unknown whether determining relative changes thresholds using the same methodology (where thresholds are determined by optimizing the mortality prediction model) instead of using the actual empiric thresholds used by KDIGO would lead to better results.

The question as to whether AKI is an event or an outcome is not answered by this paper. What is answered is the notion that AKI, as defined by absolute changes in SCr, is a good marker for poor outcomes. At this time, that absolute change in SCr is called AKI, excluding etiology and urine output from the classification. The simple use of laboratory data as described in this paper is attractive from a clinical and academic perspective. It offers an opportunity for real-time application
of absolute changes in SCr using individual patients own baseline data, and appears to be robust in predicting important outcomes (in hospital mortality). While concerns exist in using mortality as a validation for an AKI definition, it remains the most practical method to evaluate AKI on a large conceptual scale, in particular when no gold-standard exists. Neither the relative changes as proposed by KDIGO nor the delta-creatinine method proposed by Wang et al. acknowledges the aetiology of AKI. As pointed out by KDIGO guidelines and other authors, treatment and prognosis are significantly different for a stage 1 AKI from a crescentic glomerulonephritis than from a cardiogenic shock [6, 11]. Interestingly, the recent KDIGO guidelines for CKD evaluation have underscored the need for overtly describing the etiology (cause) of kidney disease, and have proposed a CGA system for describing CKD ensuring that Cause, GFR category and Albuminuria category are all defined. Similarly, the development and application of AKI definitions should not limit efforts to identify etiology of AKI and treat it accordingly. In addition, neither actual AKI criteria nor the delta-creatinine method capture the full spectrum of AKI syndrome. Patients with accelerated increase in SCr, outside the boundaries of AKI criteria, lead to the need to define a third ‘entity’ between AKI and CKD. The concept of acute kidney disease (AKD) has been proposed by KDIGO AKI working group to fill this gap, and has also been described in the new CKD guidelines [6]. The concept still requires evaluation and validation, as well as determining its utility in clinical practice.

The practical issue arising from this and other papers focused on determining the most precise definition is how to use these more consistently in clinical practice and in clinical studies. The Achilles heel of AKI research is our inability to identify the condition early, and the paucity of proven interventions to attenuate the course once established. While many investigators have identified various novel biomarkers in both urine and blood [e.g. neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin-18 (IL-18), urinary injury molecule-1 (KIM-1)], in practical terms, serum creatinine and urine output remain the parameters clinically accessible. Current treatment strategies for AKI include restoration of effective circulating fluid volume, removal of (and avoidance of) future nephrotoxins and treatment of the underlying cause of the illness which lead to AKI. Importantly, as in CKD, AKI is not a diagnosis alone, but rather a recognition of an abnormal state which is caused by other conditions.

The paper by Wang et al. adds to the literature regarding definitions of AKI, but also serves to remind us that irrespective of the definition of AKI and validation of the presence of AKI and its severity, we need to apply these definitions in a systematic way to both research and clinical care to determine the ultimate utility of them. If consistent application of a definition leads to consistent identification of the problem, and institution of all current ‘best strategies’ to attenuate the course of that condition, then this attention to getting the definition right will be worthwhile. Moving forward, as newer biomarkers are developed, and new compounds become available for testing, the nephrology community will be in a good position to evaluate these new tools and strategies. It may be time to develop some knowledge translation activities to test the clinical utility of these definitions with respect to raising awareness, so that we can move onto the more difficult task of attenuating the severity of AKI and thus improving patient outcomes.


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