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# Do novel biomarkers have utility in the diagnosis and prognosis of acute kidney injury?: PRO

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This article will present the pro-side of debate concerning the utility of novel biomarkers in the diagnosis and prognosis of acute kidney injury.



**Diagnosis of Acute Kidney Injury**

Examination of the utility of novel biomarkers for AKI diagnosis and prognosis should begin with a discussion of AKI clinical assessment without these tools. Currently, AKI is defined and staged by rapid changes in serum creatinine (SCr) or urine output (UOP).[1] These biomarkers are well known to clinicians and relatively easy to measure. SCr is also used extensively for kidney function assessment in patients with chronic kidney disease (CKD). Unfortunately, SCr has many well-documented limitations in kidney function assessment in the acute state, and cannot directly assess kidney damage, nor does it distinguish acute from chronic dysfunction.

UOP has some advantages as an acute marker because changes in urine flow may occur rapidly compared to SCr (minutes versus hours). However, UOP is neither specific to kidney injury, nor highly sensitive since forms of non-oliguric AKI (e.g., nephrotoxicity) are common. The combination of SCr and UOP provide more information than either marker alone[2, 3] but still, these traditional measures of kidney function are inadequate for assessing AKI. Clinicians therefore use a variety of additional tools to evaluate possible cases of AKI. These include imaging, urine chemistry and urine microscopy.

The presumed gold standard for AKI diagnosis is kidney biopsy, but this procedure is performed too infrequently to compare it to other diagnostic tests. When performed, evidence of acute tubular injury is usually found in patients meeting KDIGO AKI stage 2 or 3 criteria. Yet, patients without evidence of kidney disease don't undergo biopsy, so it's difficult to estimate the proportion of patients with kidney damage missed by relying on these crude functional criteria. Experimental animal AKI models that cause extensive evidence of damage on histologic examination may produce only mild or transient dysfunction. AKI often results in patchy injury with some tubules severely affected and others spared.[4]

**Damage versus Dysfunction**

With kidney damage largely unmeasurable, and dysfunction an unreliable surrogate for damage it's no surprise that clinicians have difficulty diagnosing AKI. Decreased kidney function measured by increased SCr or decreased UOP may also occur without kidney damage, for example in the setting of hypovolemia. In this setting, AKI may be purely "functional". Unfortunately, ancillary tests (e.g., imaging) are insensitive to kidney damage and may appear normal despite injury. Sometimes kidney damage can be inferred from persistent functional impairment, but the absence of persistent dysfunction does not exclude irreversible loss of nephrons because of substantial reserve capacity. Detecting kidney damage in settings where function is normal or only mildly or transiently impaired is critical because kidneys have limited capacity to regenerate. Once fibrosis has occurred, those nephrons are lost. Conversely, determining that dysfunction is not related to damage can guide management. Some AKI biomarkers were discovered by inducing kidney injury in animals and they have subsequently been established to detect damage in different parts of the human kidney.[5]

**Time**

Another critical limitation of SCr is that it may take up to 24 hours, to indicate a significant change in function. UOP may change faster, but it may not change at all and when it does it still takes some time to assess—i.e., it must be measured over at least 6 hours to determine if it is reduced. Novel biomarkers are considerably faster. Tissue inhibitor of Metaloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) are preformed molecules that are released into the urine within minutes of injury.[6] Similarly ,neutrophil gelatinase-associated lipocalin (NGAL) is upregulated and observed in the urine at 2 hours, 36 hours prior to changes in SCr for patients with AKI.[7]

Failure to detect kidney damage promptly may reduce the ability to reverse it. Existing management strategies for AKI include discontinuing offending drugs, relieving obstruction, and optimization of hemodynamics.[1] Biomarker-guided implementation of a care bundle based on the KDIGO guideline demonstrated a significant reduction in AKI events[8, 9] following cardiac

surgery and these studies have also shown that these interventions are not applied routinely in patients without AKI so the biomarker has a material impact on patient care.



**Prognosis**

AKI negatively impacts short and long-term survival. In adults, mortality in the year following AKI exceeds 25% and the rate of progression of or to CKD exceeds 20%.[10] Furthermore, AKI recures in nearly a third of patients in the year following an episode. Although not developed for this purpose, novel AKI biomarkers provide additional prognostic information over and above KDIGO-based AKI staging. Importantly, death or dialysis rates by nine months[11, 12] or by hospital discharge[13] are higher in patients with increased TIMP-2•IGFBP7 *only* when functional changes have also occurred. As such, the prognostic signal would seem to be specific to AKI and not a 'general' mortality indicator. The results are also consistent with the nature of TIMP-2 and IGFBP7 as stress rather than damage biomarkers. Stress in isolation may be benign but when it coexists with dysfunction it may signal actual damage. However, this interpretation is challenged by the work of Husain-Syed and colleagues who have demonstrated that increased urinary TIMP-2•IGFBP7 following cardiac surgery is associated with loss of renal functional reserve at three months even in the absence of AKI.[14] It may be that crude measures, such as death or dialysis, cannot detect kidney stress without dysfunction in the context of cardiac surgery that results in some degree of injury, but measuring renal functional reserve may reveal it.

Given the potential for novel biomarkers to provide information beyond KDIGO staging, the 23rd Acute Disease Quality Initiative (ADQI-23) workgroup proposed an expanded classification for AKI adding biomarkers for each stage (Table 1).[15] The first validation of this classification has been recently published using TIMP-2•IGFBP7 in adults with sepsis. In patients who developed AKI using standard functional criteria (SCr and UOP) according to KDIGO staging, the addition of urinary TIMP-2•IGFBP7 >2.0 $(ng/mL)^2/1000$ identified patients with lower 30-day survival within the functional stages. Furthermore, TIMP-2•IGFBP7 >1.0 $(ng/mL)^2/1000$ may be helpful in stratifying patients in the absence of functional criteria for AKI.

Systematic reviews of NGAL in adults and children similarly demonstrate worse outcomes (mortality and hospital LOS) in patients with both functional and structural AKI.[16, 17] While mortality rates for critically ill children are lower than those for adults, NGAL has been studied extensively to delineate functional *vs* structural *vs.* combined in children after cardiac surgery and sepsis,[18, 19] also showing worse outcomes for patients with structural or combined structural and functional AKI.

**Clinical Experience**

It's not known what proportion of physicians use novel AKI biomarkers in their clinical practice, but estimates are quite low—even among those with a critical care nephrology focus.[20] TIMP-2 and IGFBP7 were incorporated into a clinical laboratory test, the NephroCheck™ test, which received FDA approval in 2014.[21] NGAL use was first reported clinically in 2017.[22] We use these tests daily in our clinical practice and find utility in them. Most arguments against their use do not reflect experience and instead challenge whether they are accurate enough despite multiple meta-analyses concluding acceptable operating characteristics or are concerned about limitations when CKD or diverse etiologies of AKI are present.[23] However, biomarkers like TIMP-2•IGFBP7 and NGAL have been shown to perform quite well in patients CKD[24, 25] or when the etiology of AKI is sepsis,[19, 26] surgery,[27, 28] or nephrotoxins.[29, 30] Some clinicians have wondered whether interventions can be effective or even whether all available are already being applied. However, the intent of diagnostic and prognostic testing is to bring personalized medicine to the bedside. One size does not fit all for AKI any more than for other illnesses. Consensus across sub-specialties exist for personalized care in response to biomarkers[31] and various experts have already included biomarkers in standardized AKI management guidelines for cardiac surgery.[32] Others are likely to follow.

Finally, many authors appear be confused by how the costs of diagnostics tests fit into the healthcare landscape and who pays for them.[23] Novel AKI biomarkers are quite inexpensive in comparison to many other routine tests including imaging and electrophysiologic testing. Of course, they are currently more expensive than creatinine, but any new test will cost more relative to established clinical laboratory assays. In all cases, the cost of AKI itself, estimated to

be in thousands to tens of thousands[33] should be considered when evaluating the costs of tools used to prevent it.

It is thus our opinion, as clinicians, scientists, and AKI experts, that novel biomarkers such as NGAL and TIMP-2•IGFBP7 have considerable utility in the diagnosis and prognosis of AKI. This judgement is based on an extensive literature base including our own studies but also our own extensive clinical experience.

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**Table 1. Proposed new definition and staging of acute kidney injury by the ADQI-23 consensus conference.**

| KDIGO Stages | Functional criteria | Biomarkers | New Stages |
|---|---|---|---|
| **no AKI** | No increased sCr ≥ 0.3 mg/dL in ≤ 48 hours AND<br>No increased sCr ≥ 1.5 from baseline in 7 days AND<br>UO > 0.5 mL/kg/h in 6 hours period | **-** | **No AKI** |
| | | **+** | **Stage 1S** |
| **Stage 1** | Increased sCr ≥ 0.3 mg/dL in ≤ 48 hours OR<br>Increased sCr 1.5-1.9 times from baseline in < 7 days OR<br>UO < 0.5 mL/kg/h for 6-12 hours | **-** | **Stage 1A** |
| | | **+** | **Stage 1B** |
| **Stage 2** | Increased sCr 2.0-2.9 times from baseline OR<br>UO < 0.5 mL/kg/h for ≥ 12 hours | **-** | **Stage 2A** |
| | | **+** | **Stage 2B** |
| **Stage 3** | Increased sCr ≥ 3.0 times from baseline OR<br>sCr ≥ 4.0 mg/dL with acute increase of ≥ 0.3 mg/dL OR<br>UO < 0.3 mL/kg/h for ≥ 24 hours OR<br>anuria for ≥ 12 hours OR<br>initiation of renal replacement therapy | **-** | **Stage 3A** |
| | | **+** | **Stage 3B** |

Adapted from Acute Disease Quality Initiative 23 (Figure 5) on www.ADQI.org and published by Ostermann and colleagues.[a]

[a]Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference: A Consensus Statement. JAMA Netw Open. Oct 2020;3(10):e2019209. doi:10.1001/jamanetworkopen.2020.19209

AKI = acute kidney injury; KDIGO = Kidney Disease: Improving Global Outcomes; sCr = serum creatinine; UO = urinary output.

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