



Consensus Statement | Critical Care Medicine

# Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference

## A Consensus Statement

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### Abstract

**IMPORTANCE** In the last decade, new biomarkers for acute kidney injury (AKI) have been identified and studied in clinical trials. Guidance is needed regarding how best to incorporate them into clinical practice.

**OBJECTIVE** To develop recommendations on AKI biomarkers based on existing data and expert consensus for practicing clinicians and researchers.

**EVIDENCE REVIEW** At the 23rd Acute Disease Quality Initiative meeting, a meeting of 23 international experts in critical care, nephrology, and related specialties, the panel focused on 4 broad areas, as follows: (1) AKI risk assessment; (2) AKI prediction and prevention; (3) AKI diagnosis, etiology, and management; and (4) AKI progression and kidney recovery. A literature search revealed more than 65 000 articles published between 1965 and May 2019. In a modified Delphi process, recommendations and consensus statements were developed based on existing data, with 90% agreement among panel members required for final adoption. Recommendations were graded using the Grading of Recommendations, Assessment, Development and Evaluations system.

**FINDINGS** The panel developed 11 consensus statements for biomarker use and 14 research recommendations. The key suggestions were that a combination of damage and functional biomarkers, along with clinical information, be used to identify high-risk patient groups, improve the diagnostic accuracy of AKI, improve processes of care, and assist the management of AKI.

**CONCLUSIONS AND RELEVANCE** Current evidence from clinical studies supports the use of new biomarkers in prevention and management of AKI. Substantial gaps in knowledge remain, and more research is necessary.

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### Introduction

Acute kidney injury (AKI) is common in hospitalized adults and children and associated with serious complications and high health care costs. Traditionally, 2 functional biomarkers, serum creatinine (sCr) and urine output, are used to define AKI,<sup>1</sup> but these markers are limited by delayed changes following kidney injury and have low sensitivity and specificity. Several novel biomarkers have been shown to detect AKI earlier and are more sensitive than sCr (**Table**).<sup>2-19</sup> For any prevention strategies

### Key Points

**Question** How can new biomarkers for acute kidney injury be integrated into routine clinical practice?

**Findings** In this consensus statement, a 23-expert panel developed 11 recommendations for the use of new stress, functional, and damage biomarkers in clinical practice to prevent and manage acute kidney injury. In addition, gaps in knowledge and areas for more research were identified.

**Meaning** The integration of appropriately selected biomarkers in routine clinical practice has potential to improve acute kidney injury care.

### + Supplemental content

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**Table. Description and Characteristics of Common Biomarkers of AKI**

AKI biomarker	Biological role	Source	Stress marker <sup>a</sup>	Damage marker <sup>b</sup>	Functional marker <sup>c</sup>	Potential role in clinical practice		
						Risk assessment	Prediction of AKI	Diagnosis of AKI
Alanine aminopeptidase: alkaline phosphatase; γ-glutamyl transpeptidase	Enzymes located on the brush border villi of the proximal tubular cells; released into urine after tubular damage	Coca et al, <sup>2</sup> 2008		Urine		X	X	X
Calprotectin	Cytosolic calcium-binding complex; derived from neutrophils and monocytes; detectable in urine in intrinsic AKI	Charlton et al, <sup>3</sup> 2014; Heller et al, <sup>4</sup> 2011		Urine		X		
C-C motif chemokine ligand 14	Pro-inflammatory chemokine; released into urine following stress or damage of tubular cells	Hoste et al, <sup>5</sup> 2020		Urine				X
Chitinase 3-like protein 1	39 kDa intracellular protein of glycoside hydrolase family; expressed by endothelial cells, macrophages, and neutrophils	De Loor et al, <sup>6</sup> 2016		Urine and plasma		X		
Cystatin C	13 kDa cysteine protease inhibitor produced by nucleated human cells; freely filtered	Coca et al, <sup>2</sup> 2008; Ho et al, <sup>7</sup> 2015; Ravn et al, <sup>8</sup> 2019			Plasma	X	X	X
Dickkopf-3	38 kDa stress-induced, kidney tubular epithelial-derived glycoprotein; secreted into urine under tubular stress conditions	Schunk et al, <sup>9</sup> 2019	Urine			X		
α glutathione S-transferase	Cytoplasmic enzyme in proximal tubule	Koynar et al, <sup>10</sup> 2010		Urine		X		
γ glutathione S-transferase	Cytoplasmic enzyme in distal tubules	Coca et al, <sup>2</sup> 2008; Charlton et al, <sup>3</sup> 2014		Urine		X		
Hepatocyte growth factor	Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	Heller et al, <sup>4</sup> 2011; Vaidya et al, <sup>11</sup> 2008		Plasma			X	X
Hepcidin	2.78 kDa peptide hormone predominantly produced in hepatocytes; freely filtered	Ho et al, <sup>7</sup> 2015		Urine and plasma		X	X	X
Tissue metalloproteinase-2; insulin-like growth factor binding protein-7	Metalloproteinases released during cell cycle arrest	Kashani et al, <sup>12</sup> 2013; Ostermann et al, <sup>13</sup> 2018; Joannidis et al, <sup>14</sup> 2019	Urine			X	X	X
Interleukin-18	18 kDa pro-inflammatory cytokine; released into urine following tubular damage	Coca et al, <sup>2</sup> 2008; Ho et al, <sup>7</sup> 2015		Urine		X		
Kidney injury molecule-1	Transmembrane glycoprotein produced by proximal tubular cell; released into urine after tubular damage	Coca et al, <sup>2</sup> 2008; Ho et al, <sup>7</sup> 2015; Koynar et al, <sup>10</sup> 2010		Urine		X	X	X
Liver-type fatty acid-binding protein	14 kDa intracellular lipid chaperone; freely filtered and reabsorbed in proximal tubule; urinary excretion after tubular cell damage	Ho et al, <sup>7</sup> 2015		Urine and plasma		X		
MicroRNA	Endogenous single-stranded non-coding nucleotides; >50 individual microRNAs are expressed in AKI, especially in association with inflammation, apoptosis and fibrosis	Fan et al, <sup>15</sup> 2019		Urine and plasma		X		
Monocyte chemoattractant peptide-1	Peptide expressed in tubular epithelial cells, kidney mesangial cells and podocytes; released into urine	Moledina et al, <sup>16</sup> 2017		Urine			X	X
N-acetyl-β-D-glucosaminidase	>130 kDa lysosomal enzyme; released into urine after tubular damage	Charlton et al, <sup>3</sup> 2014		Urine		X		
Neutrophil gelatinase-associated lipocalin	At least 3 different types: (1) monomeric 25 kDa glycoprotein produced by neutrophils and epithelial tissues, including tubular cells; (2) homodimeric 45 kDa protein produced by neutrophils; (3) heterodimeric 135 kDa protein produced by tubular cells	Coca et al, <sup>2</sup> 2008; Ho et al, <sup>7</sup> 2015; Charlton et al, <sup>3</sup> 2014		Urine and plasma		X	X	X

(continued)

Table. Description and Characteristics of Common Biomarkers of AKI (continued)

AKI biomarker	Biological role	Source	Stress marker <sup>a</sup>	Damage marker <sup>b</sup>	Functional marker <sup>c</sup>	Potential role in clinical practice			
						Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI
Netrin-1	50-75 kDa laminin-related molecule minimally expressed in proximal tubular cells of normal kidneys; released into urine after tubular cell damage	Ramesh et al, <sup>17</sup> 2010		Urine		X			
Osteopontin	Glycoprotein expressed in tubular cells and interstitial infiltrating cells in areas of tubulointerstitial damage	Lorenzen et al, <sup>18</sup> 2011		Plasma		X	X		
Proenkephalin A	Endogenous polypeptide hormone in adrenal medulla, nervous system, immune system and renal tissue; freely filtered	Legrand et al, <sup>19</sup> 2019			Plasma		X	X	X
Retinol binding protein	21 kDa glycoprotein; synthesized by liver; filtered by glomeruli and reabsorbed by proximal tubules; released into urine following tubular damage	Charlton et al, <sup>3</sup> 2014		Plasma					
Tumor necrosis factor	Pro-inflammatory cytokine; released after tubular damage	Ho et al, <sup>7</sup> 2015		Plasma			X		

Abbreviation: AKI, acute kidney injury.

<sup>c</sup> Functional markers reflect changes in glomerular filtration.

<sup>a</sup> Stress markers indicate cell stress; cell stress can resolve or progress to damage or alter kidney function.

<sup>b</sup> Damage markers indicate structural damage that may or may not be associated with reduced kidney function. These molecules include constitutive proteins released by the damaged kidney, molecules upregulated in response to injury, or nonkidney tissue products that are filtered, reabsorbed, or secreted by the kidney.

to be effective, patients with high risk need to be identified before kidney insults result in kidney damage, and AKI needs to be diagnosed as early as possible.

In 2011, the 10th Acute Disease Quality Initiative (ADQI) meeting focused on AKI biomarkers and their application in clinical practice.<sup>20</sup> The expert committee concluded that the evidence for AKI biomarkers was limited and insufficient for recommendations and that more research and strategies toward the adoption of biomarkers in clinical practice were needed. Subsequently, new AKI biomarkers have been discovered, clinical trials have been completed, and some biomarkers have gained official regulatory approval.<sup>12,21-23</sup> In 2019, an ADQI meeting was called to review this new evidence and to develop recommendations regarding AKI risk assessment, prediction, prevention, diagnosis, management, and kidney recovery for practicing clinicians and researchers.

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## Methods

The 23rd ADQI consensus meeting followed established ADQI methods to provide statements based on existing evidence and professional judgement and to identify clinical research priorities.<sup>24</sup> The consensus process incorporated a multistep modified Delphi method. In early 2019, the steering group identified 4 broad topics (eTable 1 in the [Supplement](#)) and invited a 23-expert panel, representing nephrology, critical care medicine, surgery, anesthesia, pediatrics, clinical biochemistry, and pharmacy. The project followed the ADQI methods as outlined in this section. The article summarizes the conclusions of an international expert panel. The conclusions are based on the existing evidence in the literature. Therefore, institutional approval was not required. All panelists consented to their inclusion in this article. This report followed the Standards for Quality Improvement Reporting Excellence ([SQUIRE](#)) reporting guideline.

The working groups determined the key questions and identified relevant literature by searching PubMed, MEDLINE, Embase, the Cochrane Library, ClinicalTrials.gov, and Cochrane Controlled Trials Register, using the terms *acute kidney injury* or *AKI* and *biomarker*, combined with *risk*, *diagnosis*, *etiology*, *prevention*, *management*, *prediction*, or *prognosis*. Because of the volume of retrieved literature (>65 000 articles), representative publications were selected<sup>2,5,7,9,10,19,25-46</sup> (eTable 2 in the [Supplement](#)). Articles were eligible if they were prospective or retrospective cohort studies, case-control studies, randomized clinical trials, or systematic reviews evaluating the role of serum or urinary biomarkers for AKI. Each working group drafted recommendations and consensus statements. Recommendations were graded based on the Grading of Recommendations Assessment, Development, and Evaluation system (eTable 3 in the [Supplement](#)). At a face-to-face meeting of all 23 panelists in Padova, Italy, from May 30 to June 2, 2019, each group presented their statements and recommendations. Panel members discussed the statements until agreement was reached regarding whether to retain, modify, or eliminate them. Only panelists who attended the face-to-face meeting participated in the discussion and final approval. Statements required 90% agreement from the panel to be included in the final document. The contributions of all groups were merged and reconciled by the steering group. The final document was approved by all panelists. Here, we report the conclusions.

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## Results

### Biomarkers for AKI Risk Assessment

AKI is often already established when patients present with acute illness. Clearly, the implementation of primary prevention is not possible in these cases. However, situations in which elective clinical interventions or exposures place patients at risk of AKI provide opportunities to modify factors that contribute to AKI development and progression.

### Consensus Statement 1

The decision to perform a Kidney Health Assessment (KHA) to gauge AKI susceptibility should integrate patient factors, including demographic characteristics, comorbidities, and previous AKI episodes with the expected intensity of a planned exposure that carries AKI risk. This recommendation received a grade of B, strong.

Predisposing factors, susceptibility, and intensity of precipitating factors determine the risk of AKI. The ADQI 22 working group developed a flow diagram outlining KHA of AKI susceptibility, which incorporates previous AKI history, blood pressure, chronic kidney disease (CKD) and drugs and/or dipstick<sup>47</sup> (eFigure 1 in the [Supplement](#)). Two elective exposures that carry a particularly high AKI risk are major surgery and nephrotoxic medications.

### Consensus Statement 2

The types of functional and/or damage biomarker evaluation to be performed should be driven by the results of the KHA for AKI susceptibility. This recommendation received a grade of B, strong.

The KHA for AKI susceptibility (eFigure 1 in the [Supplement](#)) includes the assessment of CKD/creatinine and dipstick (ie, proteinuria/albuminuria) both before and after a planned exposure associated with AKI risk.<sup>47</sup> Traditional measures of kidney function include sCr, creatinine-based estimated glomerular filtration rate (eGFR) equations, serum cystatin C, cystatin plus creatinine-based eGFR equations, and selective techniques to measure GFR in high-risk patients.<sup>48</sup> Kidney damage can be assessed by estimating or measuring urinary protein excretion.<sup>29,43</sup>

New biomarkers and techniques are emerging that may allow better prediction of AKI risk.<sup>9,32</sup> A study of 733 patients who underwent cardiac surgery demonstrated that the preoperative urinary concentration of dickkopf-3, a urinary cytokine and tubular stress biomarker, predicted the development of postoperative AKI and kidney function loss with an area under the receiver operating characteristic curve (AUROC) of 0.78.<sup>9</sup>

### Consensus Statement 3

We suggest that biomarkers of acute damage are not interpretable prior to a kidney insult and should not be used for AKI risk assessment. This recommendation received a grade of A, strong.

It is unlikely that patients scheduled to undergo nephrotoxic exposures or elective surgery in stable conditions will meet the criteria for kidney stress or acute damage to be predictive of subsequent AKI. However, future AKI biomarkers in patients with specific clinical risk stratification may help to detect those at risk of kidney complications after exposure. It is also plausible that markers of kidney fitness may be discovered, including in patients with normal GFR.

## Biomarkers for AKI Prediction and Prevention

AKI affects approximately 15% of hospital admissions.<sup>49</sup> Management is mainly focused on prevention and supportive care.<sup>21</sup> In certain clinical settings, 20% to 30% of AKI cases are considered preventable.<sup>50</sup>

### Consensus Statement 4

We recommend using validated biomarkers to identify patient populations for whom preventive interventions have been shown to improve outcomes. This recommendation received a grade of A, strong.

The performance of current prediction models to identify patients at risk of AKI is variable.<sup>51-55</sup> The negative predictive value is generally good, but the positive predictive value of most models is moderate to low. In susceptible patients exposed to injurious events, validated biomarkers can predict the development or progression of AKI and may provide opportunities for intervention.<sup>21,22,28,35</sup> Trials have demonstrated that timely initiation of preventive strategies in patients with positive stress biomarkers after a kidney insult, ie, tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) were

effective at preventing AKI.<sup>21,22</sup> The patients in the Prevention of AKI trial were randomized based on patients who had an urinary concentration of TIMP-2 × IGFBP7 of at least 0.3 (ng/mL)<sup>2</sup>/1000 after cardiac surgery to protocolized vs standard care. At 72 hours, there was a 17% reduction in AKI. A similar approach was followed in the Biomarker-Guided Intervention to Prevent Acute Kidney Injury After Major Surgery study.<sup>22</sup> Patients undergoing major abdominal surgery were randomized to intervention vs standard care.<sup>22</sup> There was a 13% reduction in AKI stages 2 and 3. Similarly, the implementation of a nephrology rapid response team that used TIMP-2 × IGFBP7 monitoring to identify at-risk patients for preventative Kidney Disease Improving Global Outcomes (KDIGO) strategies reduced the need for kidney replacement therapy (KRT).<sup>56</sup>

The use of functional biomarkers may also optimize drug dosing. For decades, sCr has been used for this purpose. However, the use of sCr or any sCr-based estimate requires kidney function to be at a steady state. Cystatin C is less reliant on muscle mass and dietary intake and offers an alternative approach to estimate GFR. Reports indicate that in a steady state, eGFR estimated by creatinine–cystatin C is more precise and accurate at determining a measured GFR than eGFR estimated by creatinine or cystatin C alone.<sup>8,57</sup> The use of CKD Epidemiology Collaboration (CKD-EPI) eGFR including creatinine and cystatin C in a vancomycin dosing algorithm improved the achievement of target vancomycin trough concentrations by 22% compared with historical controls using CKD-EPI eGFR estimated with creatinine alone.<sup>58–60</sup> For life-saving drugs with potential nephrotoxic effects, the concomitant use of functional and damage biomarkers has the potential to provide important information to gauge dosing and duration of treatment and to prevent AKI.<sup>13,61</sup>

#### Consensus Statement 5

We suggest combining clinical assessment and validated biomarkers to triage patients and optimize the timing and type of interventions designed to improve processes of care and patient outcomes. This recommendation received a grade of C, strong.

Combining the clinical assessment and traditional tests with new AKI biomarkers provides information that may change processes of care and guide therapy. Negative results can be valuable, too.<sup>14,62</sup> For instance, critically ill patients with oliguria and urinary TIMP-2 × IGFBP7 of less than 0.3 (ng/mL)<sup>2</sup>/1000 do not have an increased risk of progressing to more severe AKI.<sup>14</sup> Repeated biomarker testing may be relevant, too, depending on the change in patient risk profile.

#### Biomarkers for AKI Diagnosis, Etiology, and Management

There is a persistent unmet need for an earlier identification of patients with AKI. Furthermore, diagnostic tools that identify the location, mechanism, etiology, severity, and prognosis of AKI are necessary.<sup>63</sup>

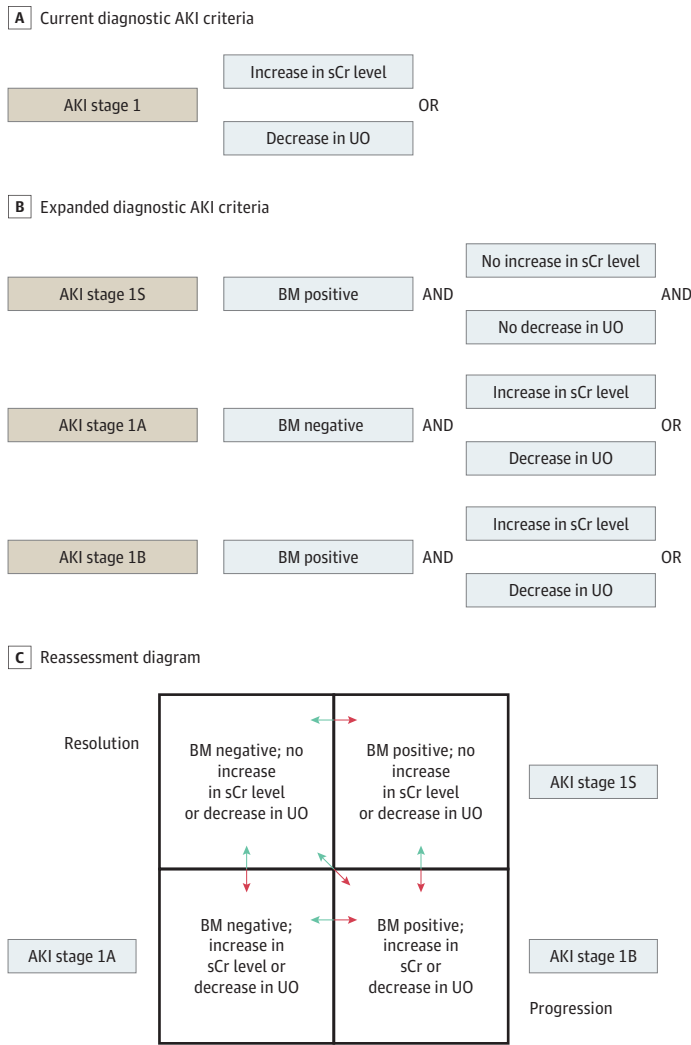
#### Consensus Statement 6

We suggest that a combination of damage and functional biomarkers, along with clinical information, be used to improve the diagnostic accuracy of AKI, to recognize the different pathophysiological processes, to discriminate AKI etiology, and to assess AKI severity. This recommendation received a grade of B, conditional.

The discovery of specific biomarkers of kidney injury has enabled a more precise delineation of the pathophysiology, site, mechanisms, and severity of injury<sup>64,65</sup> (Table). Some patients with positive damage biomarkers do not fulfill traditional AKI criteria yet have worse outcomes.<sup>23</sup> We propose that clinical information enriched by damage and functional biomarkers could lead to more sensitive AKI definitions. We therefore suggest a modification of KDIGO stage 1 AKI to reflect 3 substages (ie, 1S, 1A, and 1B) and to subcategorize stages 2 and 3 AKI by presence of biomarkers (**Figure 1** and **Figure 2**). Stage 1S identifies an early stage when there is evidence of kidney injury that is not detected by creatinine and urine output criteria. For example, in 345 children undergoing cardiopulmonary bypass,<sup>25</sup> the combination of functional (cystatin C) and damage (neutrophil gelatinase-associated lipocalin [NGAL]) biomarkers was superior to sCr in predicting the severity and

persistence of AKI. More recently, a study of 178 children<sup>41</sup> showed that those with elevated urine NGAL (uNGAL) concentrations without increased sCr levels had an almost 4-fold increased risk of all-stage AKI on day 3 compared with those without an uNGAL and sCr increase (uNGAL negative and sCr negative). Similarly, compared with patients who had no increase in uNGAL concentrations but

Figure 1. Refined Staging System for the Diagnosis of Acute Kidney Injury (AKI)



Patients with a biomarker (BM) of injury positivity without increase or decrease in serum creatinine (sCr) level and not reaching urine output (UO) criteria should be classified as stage 1S. Reassessment should be performed according to patient clinical context and temporal trends. Patients reaching sCr and UO criteria with no increase on BM are defined as stage 1A, and those reaching sCr and UO criteria with increased BM are reclassified as stage 1B. BM positivity should be based on its mechanism and defined threshold. Reprinted from Acute Disease Quality Initiative 23 and used with permission.

Figure 2. Proposed New Definition of Acute Kidney Injury

Functional criteria	Stage	Damage criteria
No change or sCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of sCr level by $\geq 0.3$ mg/dL for $\leq 48$ h or $\geq 150\%$ for $\leq 7$ days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of sCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of sCr level by >300% ( $\geq 4.0$ mg/dL with an acute increase of $\geq 0.5$ mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

Functional markers include serum creatinine (sCr) and urine output (UO) but new functional markers may also be included. Reprinted from Acute Disease Quality Initiative 23 and used with permission. To convert sCr to millimoles per liter, multiply by 88.4. KRT indicates kidney replacement therapy.

an increase in sCr levels, patients who had uNGAL and sCr increases had a 12-fold increased risk of AKI stage 2 or 3 on day 3.

TIMP-2 and IGFBP7 have also been shown to improve risk stratification in critically ill patients with AKI stage 1.<sup>14</sup> Evaluation of longer-term outcomes demonstrated that the associated risks of TIMP-2 × IGFBP7 of greater than 2.0 (ng/mL)<sup>2</sup>/1000 were equivalent to AKI progression even in instances in which no progression from AKI stage 1 was seen based on sCr and urine output. The ability to recognize the various pathophysiological processes mediating AKI will likely be critical in developing targeted therapies and designing pharmacological trials.<sup>38,66</sup>

### Consensus Statement 7

We suggest that a combination of biomarkers may assist the planning of therapy and management of AKI. This recommendation received a grade of C, conditional.

Uncertainty regarding when kidney injury actually occurred is common. Biomarkers may be able to provide guidance in determining the onset and presence of kidney damage so that potential therapies can be initiated before the injury becomes irreversible<sup>67</sup> (eFigure 2 in the [Supplement](#)). Multiple biomarkers have the potential to shed light on the pathophysiology and provide an early detection system superior to creatinine.<sup>36,68</sup>

Biomarker-guided algorithms and goal-directed management protocols appear to provide benefit in preventing and/or mitigating AKI.<sup>21,22,56,69,70</sup> For instance, if biomarkers indicate kidney stress before permanent damage occurs, there is the possibility of reversing AKI<sup>21,22</sup> (eFigure 2 in the [Supplement](#)). Consequently, embedding biomarkers within goal-directed management protocols has the potential to affect AKI recovery.<sup>70</sup>

### Consensus Statement 8

Inclusion of biomarker data with clinical assessments can be used to identify patients who will need KRT and facilitate optimal timing of KRT initiation. The recommendation received a grade of C, conditional.

Currently, the decision to start KRT is based on clinical judgement and conventional criteria. Several studies have evaluated different biomarkers in predicting the need for KRT with variable results.<sup>34</sup> In a meta-analysis of more than 15 000 patients,<sup>34</sup> the pooled AUROCs for urine and blood NGAL for prediction of KRT were 0.72 (95% CI, 0.64-0.80) and 0.76 (95% CI, 0.71-0.80), respectively, while sCr and cystatin C had pooled AUROCs of 0.76 (95% CI, 0.73-0.80) and 0.77 (95% CI, 0.73-0.81), respectively. Urine biomarkers interleukin-18, cystatin C, and TIMP-2 × IGFBP7 showed pooled AUROCs of 0.67 (95% CI, 0.61-0.73), 0.72 (95% CI, 0.58-0.87), and 0.86 (95% CI, 0.79-0.93), respectively.<sup>34</sup> Some limitations for biomarker-based predictions are the variable cutoffs, the reliance on single measurements, and confounding by underlying comorbidities and clinical conditions.

The furosemide stress test (FST) has been proposed as a means to predict the need for KRT after kidney transplantation and in patients with AKI.<sup>71,72</sup> Clinical risk scores predicting KRT are available for specific situations, ie, after cardiac surgery, but biomarkers of kidney damage have not been incorporated. In patients receiving mechanical ventilation, sCr combined with normalized urine NGAL (nuNGAL) and serum cystatin C combined with either nuNGAL or uNGAL were found to be the best predictors for KRT initiation (AUROC = 0.80).<sup>40</sup> Among patients without AKI on intensive care unit admission, the combination of serum cystatin C and Acute Physiology and Chronic Health Evaluation score performed best (AUROC = 0.78). In 2 randomized clinical trials, plasma NGAL failed to enrich the prediction for early KRT initiation.<sup>46,73</sup> Future studies should incorporate sequential assessments of both functional and damage biomarkers in patients identified as having high risk for needing KRT based on clinical risk scores.

Most studies evaluating the role of biomarkers to guide KRT discontinuation have relied on urine output, urinary Cr, or urea clearance.<sup>74</sup> The FST has also been shown to predict discontinuation of KRT (AUROC = 0.84).<sup>75</sup> An observational study<sup>33</sup> explored the role of serum cystatin C and NGAL in

110 patients at the time of cessation of continuous renal replacement therapy (CRRT). Patients who successfully discontinued CRRT had lower serum cystatin C levels and higher urine output at CRRT cessation than those who had to restart KRT. However, sCr and NGAL levels were not significantly lower in the group that recovered compared with patients in whom CRRT was restarted. Another study of 110 critically ill patients on CRRT<sup>27</sup> showed that serum NGAL was predictive of successful discontinuation of CRRT in patients with AKI but no sepsis whereas urine output was a significant predictor in patients with AKI with sepsis. Collective data suggest that there is currently limited evidence to support the use of any individual biomarker for predicting successful KRT cessation.

### Biomarkers to Assess AKI Progression and Kidney Recovery

Studies have found that complete and sustained reversal of AKI episodes within 48 to 72 hours of onset was associated with better outcomes than persistent AKI; however, different definitions for persistent AKI were applied.<sup>76</sup> Thus the ADQI 16 working group proposed defining persistent AKI as AKI that lasts more than 48 hours and recommended the use of biomarkers to risk stratify patients for whom additional workup and evaluation might be warranted.<sup>77</sup>

#### Consensus Statement 9

We suggest that novel biomarkers can be used for prediction of duration and recovery of AKI. This recommendation received a grade of C, weak.

Among patients with community-acquired pneumonia enrolled in the Genetic and Inflammatory Markers of Sepsis cohort,<sup>42</sup> the predictive value of plasma NGAL concentrations on day 1 on kidney recovery was investigated in 181 patients with severe AKI. Recovery was defined as being alive and not requiring KRT at hospital discharge. Plasma NGAL alone predicted nonrecovery of kidney function (AUROC = 0.74). However, when compared with a clinical model, plasma NGAL did not augment risk prediction.

The performance of plasma proenkephalin-A was evaluated in 956 patients with sepsis who were enrolled in the multicenter Albumin Italian Outcome Sepsis trial.<sup>26</sup> Among the subgroup of 255 patients with a sCr level of 2.0mg/dL (to convert to millimoles per liter, multiply by 88.4) on the first day, 31% had an improvement in kidney function within 48 hours. Median (interquartile range) sCr level on day 1 was significantly lower in patients who recovered kidney function within 48 hours compared with those who did not recover (2.9 [2.5-3.3] mg/dL vs 3.2 [2.6-4.2] mg/dL;  $P = .006$ ). Their median (interquartile range) day 1 plasma proenkephalin-A concentration was also significantly lower (137 [89-188] pmol/L) compared with patients without kidney recovery (226 [145-352] pmol/L). A study in patients with septic AKI<sup>31</sup> showed significantly higher proenkephalin-A concentrations in patients with major adverse kidney events, patients with persistent AKI, and those who had worsening of kidney function. The increase in proenkephalin-A concentrations preceded elevation of sCr levels in patients with worsening kidney function. A 2020 study of 331 critically ill patients with AKI stage 2 or 3 demonstrated that urinary C-C motif chemokine ligand 14 was predictive of persistent AKI.<sup>5</sup> Finally, in 733 patients undergoing cardiac surgery,<sup>9</sup> preoperative ratio of urinary dickkopf-3 to creatinine concentrations greater than 471 pg/mg was associated with a significantly higher risk of persistent kidney dysfunction (odds ratio, 6.67; 95% CI, 1.67-26.61;  $P = .007$ ) and dialysis dependency (odds ratio, 13.57; 95% CI, 1.50-122.77;  $P = .02$ ) after 90 days compared with a ratio of 471 pg/mg or less.<sup>9</sup>

#### Consensus Statement 10

Currently there is insufficient evidence to recommend the routine use of novel biomarkers to refine acute kidney disease (AKD) staging. This recommendation received a grade of C, strong.

AKD describes acute or subacute damage and/or loss of kidney function for a duration as long as 90 days<sup>77</sup> (Figure 3). To date, no study has evaluated the predictive value of novel biomarkers for AKD staging and subsequent outcomes.

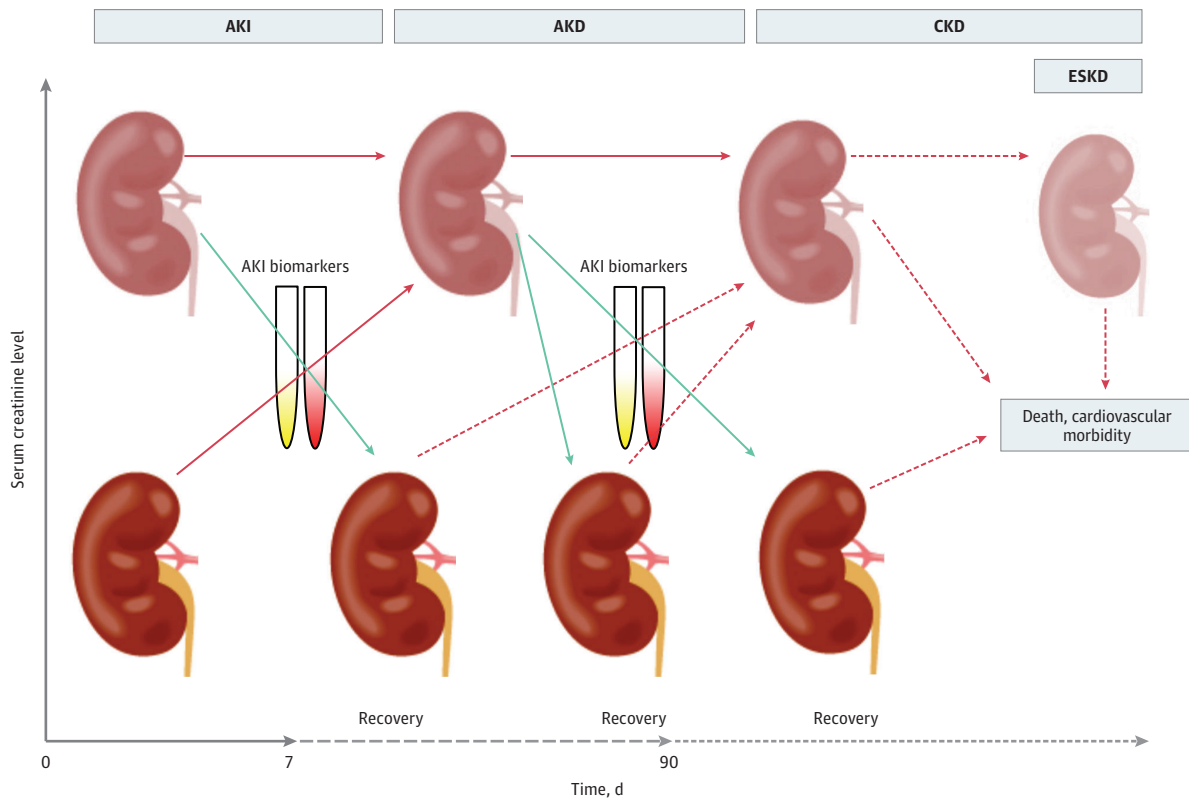
**Consensus Statement 11**

We recommend that biomarkers predictive of CKD staging and progression be incorporated into a comprehensive post-AKI/AKD care bundle and KHA. This recommendation received a grade of C, strong.

Studies have evaluated the long-term prognostic value of biomarkers for predicting KRT dependence and death among critically ill patients with AKI. Serum creatinine has a very limited role as a biomarker for kidney function in patients receiving KRT. A study using the Biological Markers of Recovery for the Kidney cohort<sup>78</sup> found increased concentrations of plasma interleukin (IL) 8 and IL-18 and tumor necrosis factor receptor type 1 (TNFR-I) on day 1 were independently associated with slower kidney recovery by day 60 among critically ill patients treated with KRT. In an analysis of multiple markers simultaneously,<sup>78</sup> increased IL-8 and TNFR-I in combination were associated with slower recovery and increased IL-8, migration inhibitory factor, and TNFR-I concentrations were associated with mortality. Using the same cohort, higher day 8 concentrations of plasma IL-6, IL-8, IL-18, IL-10, TNFR-I, and TNFR-II were associated with lower kidney recovery, and plasma concentrations of IL-6, IL-8, IL-10, IL-18, migration inhibitory factor, TNFR-I, and death receptor 5 were associated with mortality among patients receiving KRT.<sup>78</sup>

Another study<sup>44</sup> evaluated serum osteopontin, IL-6, and cystatin C for kidney recovery among 102 patients with AKI requiring KRT. Lower levels of osteopontin and IL-6 were associated with greater odds of 60-day survival with AUROCs of 0.81 and 0.74, respectively. The AUROC value for predicting survival reached its highest level when all biomarkers were combined with urine output and urinary and serum sCr upon discontinuation of KRT (AUROC = 0.88).

**Figure 3. Transition From Acute Kidney Injury (AKI) to Recovery, Acute Kidney Disease (AKD), or Chronic Kidney Disease (CKD)**



Biomarkers of kidney damage and function can refine the prediction of rapid recovery (ie, transient AKI) or persistent AKI. AKD is assessed between 7 and 90 days after an acute event. Prior to day 7, AKI criteria may still be reached, and after 90 days, CKD criteria are applicable. Scarce data suggest that new biomarkers of kidney damage and

function can refine the prediction of poor outcomes (ie, death, chronic kidney disease) at intensive care unit discharge compared to serum creatinine. Reprinted from Acute Disease Quality Initiative 23 used with permission. ESKD indicates end-stage kidney disease.

In patients receiving KRT, a higher cystatin C value at discontinuation of KRT was independently predictive of chronic dialysis.<sup>45</sup> Urinary concentrations of TIMP-2  $\times$  IGFBP7 of greater than 0.3 (ng/mL)<sup>2</sup>/1000, compared with 0.3 (ng/mL)<sup>2</sup>/1000, have also been shown to be associated with death or KRT in patients with AKI (hazard ratio, 2.16; 95% CI, 1.32-3.53).<sup>37</sup> More recently, the FROG-ICU study evaluated the prognostic utility of different AKI biomarkers obtained at intensive care unit discharge on 1-year outcome in 1207 intensive care unit survivors.<sup>19</sup> Of 460 patients with AKI, 58 patients (12.6%) were identified as having AKD at intensive care unit discharge. Most patients with AKI in the intensive care unit had elevated biomarkers of kidney damage at discharge even with apparent recovery based on sCr level. However, the predictive value for 1-year mortality was only modest (AUROC range, 0.61-0.70).

## Discussion

We have provided recommendations for the use of AKI biomarkers in routine clinical practice. However, there are still a substantial number of knowledge gaps that need to be covered in future studies (Box).

### Box. Research Recommendations

1. Studies need to be performed to determine whether novel AKI biomarkers offer additional benefit in assessment of AKI risk prior to a planned nephrotoxic exposure.
2. Appropriate performance of candidate biomarkers should be evaluated for optimal results of preventive measures guided by biomarkers, in particular:
  - a. the role of damage biomarkers to prevent AKI after specific exposures (ie, drugs) needs further investigation;
  - b. the cost-effectiveness of using biomarkers to predict and prevent AKI needs further evaluation; and
  - c. the time course, cutoffs, and interactions between functional and damage biomarkers of AKI should be further assessed.
3. Studies should investigate the role of single vs serial measurements of biomarkers in the prediction of AKI and the impact of preventive measures.
4. Research is necessary to investigate the role of nonkidney biomarkers (eg, procalcitonin, natriuretic peptide, troponin) to identify patient populations at risk for AKI.
5. We suggest further research on whether a combination of validated biomarkers can help improve the detection of etiology and the management of AKI.
6. We suggest further research on how the inherent characteristics of biomarkers (including temporal patterns) affect the understanding of the process leading to AKI, its complications, and recovery.
7. Investigations should focus on determining whether a change in serum creatinine/oliguria without change of damage biomarker is associated with worse kidney and patient outcomes.
8. Investigations should focus on determining whether elevation in biomarkers without any changes in serum creatinine/oliguria is associated with worse kidney and patient outcomes.
9. The role of serial biomarker testing should be compared with real-time glomerular filtration rate measurement.
10. Future studies are needed to evaluate the combination of damage and functional biomarkers with clinical assessments to determine the risk profiles of patients who may need kidney replacement therapy.
11. Research is needed to evaluate the utility of dynamic assessment of functional and structural markers correlated with clinical data to define the optimal timing for initiating and stopping kidney replacement therapy.
12. Studies have identified a number of candidate biomarkers and diagnostics for persistent AKI and kidney recovery. We recommend prospective validation of these novel biomarkers for prediction of persistent AKI and kidney recovery. These biomarkers should also be evaluated for their ability to improve patient management alone or in combination.
13. We recommend prospective validation of candidate biomarkers for acute kidney disease staging and prognosis and to predict successful kidney replacement therapy discontinuation.
14. We recommend prospective validation of candidate biomarkers, in combination with clinical assessment tools for the prediction of chronic kidney disease staging and longer-term outcomes after AKI or acute kidney disease.

Abbreviation: AKI, acute kidney injury.

## Limitations

This study has limitations. Our recommendations are based on existing evidence and consensus but we did not perform a systematic review of all individual studies. We also acknowledge that further biomarker studies are in progress or have been completed since the ADQI meeting was held and that it is possible that the results would affect our recommendations.

## Conclusions

Considerable progress has been made in the field of AKI biomarkers, which has resulted in a better understanding of the pathophysiology of AKI and improved outcomes with biomarker-guided management. Our consensus recommendations based on existing data aim to assist clinicians at the bedside. We acknowledge that the current literature contains some bias and limitations, and further research is needed. However, the prospect of clearer identification of high-risk patients and different AKI subphenotypes and the integration of appropriately selected biomarkers in routine clinical practice hold the key to further improvement in AKI care.

## ARTICLE INFORMATION

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## REFERENCES

1. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*. 2012;2(1):1-138. doi:10.1038/kisup.2012.1
2. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int*. 2008;73(9):1008-1016. doi:10.1038/sj.ki.5002729
3. Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. *Nephrol Dial Transplant*. 2014;29(7):1301-1311. doi:10.1093/ndt/gft510
4. Heller F, Frischmann S, Grünbaum M, Zidek W, Westhoff TH. Urinary calprotectin and the distinction between prerenal and intrinsic acute kidney injury. *Clin J Am Soc Nephrol*. 2011;6(10):2347-2355. doi:10.2215/CJN.02490311
5. Hoste E, Bihorac A, Al-Khafaji A, et al; RUBY Investigators. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. *Intensive Care Med*. 2020;46(5):943-953. doi:10.1007/s00134-019-05919-0
6. De Loor J, Decruyenaere J, Demeyere K, Nuytinck L, Hoste EA, Meyer E. Urinary chitinase 3-like protein 1 for early diagnosis of acute kidney injury: a prospective cohort study in adult critically ill patients. *Crit Care*. 2016;20:38. doi:10.1186/s13054-016-1192-x
7. Ho J, Tangri N, Komenda P, et al. Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: a meta-analysis. *Am J Kidney Dis*. 2015;66(6):993-1005. doi:10.1053/j.ajkd.2015.06.018
8. Ravn B, Rimes-Stigare C, Bell M, et al. Creatinine versus cystatin C based glomerular filtration rate in critically ill patients. *J Crit Care*. 2019;52:136-140. doi:10.1016/j.jcrc.2019.04.007
9. Schunk SJ, Zarbock A, Meersch M, et al. Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study. *Lancet*. 2019;394(10197):488-496. doi:10.1016/S0140-6736(19)30769-X
10. Koyner JL, Vaidya VS, Bennett MR, et al. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. *Clin J Am Soc Nephrol*. 2010;5(12):2154-2165. doi:10.2215/CJN.00740110
11. Vaidya VS, Waikar SS, Ferguson MA, et al. Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. *Clin Transl Sci*. 2008;1(3):200-208. doi:10.1111/j.1752-8062.2008.00053.x
12. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17(1):R25. doi:10.1186/cc12503
13. Ostermann M, McCullough PA, Forni LG, et al; all SAPHIRE Investigators. Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. *Crit Care Med*. 2018;46(3):375-383. doi:10.1097/CCM.0000000000002847
14. Joannidis M, Forni LG, Haase M, et al; Sapphire Investigators. Use of cell cycle arrest biomarkers in conjunction with classical markers of acute kidney injury. *Crit Care Med*. 2019;47(10):e820-e826. doi:10.1097/CCM.0000000000003907
15. Fan PC, Chen CC, Peng CC, et al. A circulating miRNA signature for early diagnosis of acute kidney injury following acute myocardial infarction. *J Transl Med*. 2019;17(1):139. doi:10.1186/s12967-019-1890-7
16. Moledina DG, Isguven S, McArthur E, et al; Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) Consortium. Plasma monocyte chemotactic protein-1 is associated with acute kidney injury and death after cardiac operations. *Ann Thorac Surg*. 2017;104(2):613-620. doi:10.1016/j.athoracsur.2016.11.036
17. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P. Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Clin J Am Soc Nephrol*. 2010;5(3):395-401. doi:10.2215/CJN.05140709
18. Lorenzen JM, Hafer C, Faulhaber-Walter R, et al. Osteopontin predicts survival in critically ill patients with acute kidney injury. *Nephrol Dial Transplant*. 2011;26(2):531-537. doi:10.1093/ndt/gfq498
19. Legrand M, Hollinger A, Vieillard-Baron A, et al; French and euRopean Outcome reGistry in ICUs (FROG-ICU) Investigators. One-year prognosis of kidney injury at discharge from the ICU: a multicenter observational study. *Crit Care Med*. 2019;47(12):e953-e961. doi:10.1097/CCM.0000000000004010
20. Murray PT, Mehta RL, Shaw A, et al; ADQI 10 workgroup. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. *Kidney Int*. 2014;85(3):513-521. doi:10.1038/ki.2013.374

21. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med*. 2017;43(11):1551-1561. doi:10.1007/s00134-016-4670-3
22. Göcze I, Jauch D, Götz M, et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. *Ann Surg*. 2018;267(6):1013-1020. doi:10.1097/SLA.0000000000002485
23. Haase M, Devarajan P, Haase-Fielitz A, et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol*. 2011;57(17):1752-1761. doi:10.1016/j.jacc.2010.11.051
24. Kellum JA, Bellomo R, Ronco C. Acute Dialysis Quality Initiative (ADQI): methodology. *Int J Artif Organs*. 2008;31(2):90-93. doi:10.1177/039139880803100202
25. Basu RK, Wong HR, Krawczeski CD, et al. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. *J Am Coll Cardiol*. 2014;64(25):2753-2762. doi:10.1016/j.jacc.2014.09.066
26. Caironi P, Latini R, Struck J, et al; ALBIOS Study Investigators. Circulating proenkephalin, acute kidney injury, and its improvement in patients with severe sepsis or shock. *Clin Chem*. 2018;64(9):1361-1369. doi:10.1373/clinchem.2018.288068
27. Chen X, Chen Z, Wei T, Li P, Zhang L, Fu P. The effect of serum neutrophil gelatinase-associated lipocalin on the discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury. *Blood Purif*. 2019;48(1):10-17. doi:10.1159/000499026
28. Engelman DT, Crisafi C, Germain M, et al. Using urinary biomarkers to reduce acute kidney injury following cardiac surgery. *J Thorac Cardiovasc Surg*. 2019;S0022-5223(19)32245-7. doi:10.1016/j.jtcvs.2019.10.034
29. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol*. 2010;21(10):1757-1764. doi:10.1681/ASN.2010010128
30. Hodgson LE, Venn RM, Short S, et al. Improving clinical prediction rules in acute kidney injury with the use of biomarkers of cell cycle arrest: a pilot study. *Biomarkers*. 2019;24(1):23-28. doi:10.1080/1354750X.2018.1493617
31. Hollinger A, Wittebole X, François B, et al. Proenkephalin A 119-159 (Penkid) is an early biomarker of septic acute kidney injury: the Kidney in Sepsis and Septic Shock (Kid-SSS) Study. *Kidney Int Rep*. 2018;3(6):1424-1433. doi:10.1016/j.ekir.2018.08.006
32. Husain-Syed F, Ferrari F, Sharma A, et al. Preoperative renal functional reserve predicts risk of acute kidney injury after cardiac operation. *Ann Thorac Surg*. 2018;105(4):1094-1101. doi:10.1016/j.athoracsur.2017.12.034
33. Kim CS, Bae EH, Ma SK, Kim SW. A prospective observational study on the predictive value of serum cystatin C for successful weaning from continuous renal replacement therapy. *Kidney Blood Press Res*. 2018;43(3):872-881. doi:10.1159/000490335
34. Klein SJ, Brandtner AK, Lehner GF, et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med*. 2018;44(3):323-336. doi:10.1007/s00134-018-5126-8
35. Kane-Gill SL, Peerapornratana S, Wong A, et al. Use of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 [TIMP2]•[IGFBP7] as an AKI risk screening tool to manage patients in the real-world setting. *J Crit Care*. 2020;57:97-101. doi:10.1016/j.jcrc.2020.02.002
36. Koyner JL, Garg AX, Coca SG, et al; TRIBE-AKI Consortium. Biomarkers predict progression of acute kidney injury after cardiac surgery. *J Am Soc Nephrol*. 2012;23(5):905-914. doi:10.1681/ASN.2011090907
37. Koyner JL, Shaw AD, Chawla LS, et al; Sapphire Investigators. Tissue inhibitor metalloproteinase-2 (TIMP-2)•IGF-binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI. *J Am Soc Nephrol*. 2015;26(7):1747-1754. doi:10.1681/ASN.2014060556
38. Moledina DG, Wilson FP, Poher JS, et al. Urine TNF- $\alpha$  and IL-9 for clinical diagnosis of acute interstitial nephritis. *JCI Insight*. 2019;4(10):127456. doi:10.1172/jci.insight.127456
39. Murugan R, Wen X, Shah N, et al; Biological Markers for Recovery of Kidney (BioMaRK) Study Investigators. Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy. *Nephrol Dial Transplant*. 2014;29(10):1854-1864. doi:10.1093/ndt/gfu051
40. Pipili C, Ioannidou S, Tripodaki ES, et al. Prediction of the renal replacement therapy requirement in mechanically ventilated critically ill patients by combining biomarkers for glomerular filtration and tubular damage. *J Crit Care*. 2014;29(4):692.e7-692.e13. doi:10.1016/j.jcrc.2014.02.011

41. Stanski N, Menon S, Goldstein SL, Basu RK. Integration of urinary neutrophil gelatinase-associated lipocalin with serum creatinine delineates acute kidney injury phenotypes in critically ill children. *J Crit Care*. 2019;53:1-7. doi:10.1016/j.jcrc.2019.05.017
42. Srisawat N, Murugan R, Lee M, et al; Genetic and Inflammatory Markers of Sepsis (GenIMS) Study Investigators. Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. *Kidney Int*. 2011;80(5):545-552. doi:10.1038/ki.2011.160
43. Wahl TS, Graham LA, Morris MS, et al. Association between preoperative proteinuria and postoperative acute kidney injury and readmission. *JAMA Surg*. 2018;153(9):e182009. doi:10.1001/jamasurg.2018.2009
44. Yang T, Sun S, Zhao Y, et al. Biomarkers upon discontinuation of renal replacement therapy predict 60-day survival and renal recovery in critically ill patients with acute kidney injury. *Hemodial Int*. 2018;22(1):56-65. doi:10.1111/hdi.12532
45. Yang T, Sun S, Lin L, et al. Predictive factors upon discontinuation of renal replacement therapy for long-term chronic dialysis and death in acute kidney injury patients. *Artif Organs*. 2017;41(12):1127-1134. doi:10.1111/aor.12927
46. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315(20):2190-2199. doi:10.1001/jama.2016.5828
47. Kashani K, Rosner MH, Haase M, et al. Quality improvement goals for acute kidney injury. *Clin J Am Soc Nephrol*. 2019;14(6):941-953. doi:10.2215/CJN.01250119
48. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. *Am J Kidney Dis*. 2013;62(3):595-603. doi:10.1053/j.ajkd.2013.03.027
49. Lewington AJ, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int*. 2013;84(3):457-467. doi:10.1038/ki.2013.153
50. Joslin J, Wilson H, Zubli D, et al. Recognition and management of acute kidney injury in hospitalised patients can be partially improved with the use of a care bundle. *Clin Med (Lond)*. 2015;15(5):431-436. doi:10.7861/clinmedicine.15-5-431
51. Basu RK, Kaddourah A, Goldstein SL; AWARE Study Investigators. Assessment of a renal angina index for prediction of severe acute kidney injury in critically ill children: a multicentre, multinational, prospective observational study. *Lancet Child Adolesc Health*. 2018;2(2):112-120. doi:10.1016/S2352-4642(17)30181-5
52. Chiofolo C, Chbat N, Ghosh E, Eshelman L, Kashani K. Automated continuous acute kidney injury prediction and surveillance: a random forest model. *Mayo Clin Proc*. 2019;94(5):783-792. doi:10.1016/j.mayocp.2019.02.009
53. Koyner JL, Adhikari R, Edelson DP, Churpek MM. Development of a multicenter ward-based AKI prediction model. *Clin J Am Soc Nephrol*. 2016;11(11):1935-1943. doi:10.2215/CJN.00280116
54. Koyner JL, Carey KA, Edelson DP, Churpek MM. The development of a machine learning inpatient acute kidney injury prediction model. *Crit Care Med*. 2018;46(7):1070-1077. doi:10.1097/CCM.0000000000003123
55. Malhotra R, Kashani KB, Macedo E, et al. A risk prediction score for acute kidney injury in the intensive care unit. *Nephrol Dial Transplant*. 2017;32(5):814-822. doi:10.1093/ndt/gfx026
56. Rizo-Topete LM, Rosner MH, Ronco C. Acute kidney injury risk assessment and the nephrology rapid response team. *Blood Purif*. 2017;43(1-3):82-88. doi:10.1159/000452402
57. Rimes-Stigare C, Ravn B, Awad A, et al. Creatinine- and cystatin C-based incidence of chronic kidney disease and acute kidney disease in AKI survivors. *Crit Care Res Pract*. 2018;2018:7698090. doi:10.1155/2018/7698090
58. Frazee EN, Rule AD, Herrmann SM, et al. Serum cystatin C predicts vancomycin trough levels better than serum creatinine in hospitalized patients: a cohort study. *Crit Care*. 2014;18(3):R110. doi:10.1186/cc13899
59. Frazee E, Rule AD, Lieske JC, et al. Cystatin C-guided vancomycin dosing in critically ill patients: a quality improvement project. *Am J Kidney Dis*. 2017;69(5):658-666. doi:10.1053/j.ajkd.2016.11.016
60. Barreto EF, Rule AD, Murad MH, et al. Prediction of the renal elimination of drugs with cystatin C vs creatinine: a systematic review. *Mayo Clin Proc*. 2019;94(3):500-514. doi:10.1016/j.mayocp.2018.08.002
61. Barreto EF, Rule AD, Voils SA, Kane-Gill SL. Innovative use of novel biomarkers to improve the safety of renally eliminated and nephrotoxic medications. *Pharmacotherapy*. 2018;38(8):794-803. doi:10.1002/phar.2149
62. Murray PT, Wettersten N, van Veldhuisen DJ, et al. Utility of urine neutrophil gelatinase-associated lipocalin for worsening renal function during hospitalization for acute heart failure: primary findings of the Urine N-gal Acute Kidney Injury N-gal Evaluation of Symptomatic Heart Failure Study (AKINESIS). *J Card Fail*. 2019;25(8):654-665. doi:10.1016/j.cardfail.2019.05.009
63. Mårtensson J, Martling CR, Bell M. Novel biomarkers of acute kidney injury and failure: clinical applicability. *Br J Anaesth*. 2012;109(6):843-850. doi:10.1093/bja/aes357

64. Singh R, Dodkins J, Doyle JF, Forni LG. Acute kidney injury biomarkers: what do they tell us? *Contrib Nephrol*. 2018;193:21-34. doi:10.1159/000484960
65. Endre ZH, Kellum JA, Di Somma S, et al. Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol*. 2013;182:30-44. doi:10.1159/000349964
66. Okusa MD, Rosner MH, Kellum JA, Ronco C; Acute Dialysis Quality Initiative XIII Workgroup. Therapeutic targets of human AKI: harmonizing human and animal AKI. *J Am Soc Nephrol*. 2016;27(1):44-48. doi:10.1681/ASN.2015030233
67. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. *Clin Chem Lab Med*. 2017;55(8):1074-1089. doi:10.1515/cclm-2016-0973
68. Kane-Gill SL, Smithburger PL, Kashani K, Kellum JA, Frazee E. Clinical relevance and predictive value of damage biomarkers of drug-induced kidney injury. *Drug Saf*. 2017;40(11):1049-1074. doi:10.1007/s40264-017-0565-7
69. Berdugo MA, Kirson NY, Zimmer L, et al. Economic and clinical benefits of early identification of acute kidney injury using a urinary biomarker. *J Med Econ*. 2019;22(12):1281-1289. doi:10.1080/13696998.2019.1636053
70. Guzzi LM, Bergler T, Binnall B, et al. Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel. *Crit Care*. 2019;23(1):225. doi:10.1186/s13054-019-2504-8
71. McMahon BA, Koyner JL, Novick T, et al. The prognostic value of the furosemide stress test in predicting delayed graft function following deceased donor kidney transplantation. *Biomarkers*. 2018;23(1):61-69. doi:10.1080/1354750X.2017.1387934
72. Lumlertgul N, Peerapornratana S, Trakarnvanich T, et al; FST Study Group. Early versus standard initiation of renal replacement therapy in furosemide stress test non-responsive acute kidney injury patients (the FST trial). *Crit Care*. 2018;22(1):101. doi:10.1186/s13054-018-2021-1
73. Wald R, Adhikari NK, Smith OM, et al; Canadian Critical Care Trials Group. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int*. 2015;88(4):897-904. doi:10.1038/ki.2015.184
74. Schiffli H. Discontinuation of renal replacement therapy in critically ill patients with severe acute kidney injury: predictive factors of renal function recovery. *Int Urol Nephrol*. 2018;50(10):1845-1851. doi:10.1007/s11255-018-1947-1
75. van der Voort PH, Boerma EC, Pickkers P. The furosemide stress test to predict renal function after continuous renal replacement therapy. *Crit Care*. 2014;18(3):429. doi:10.1186/cc13871
76. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G. Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol*. 2015;26(9):2231-2238. doi:10.1681/ASN.2014070724
77. Chawla LS, Bellomo R, Bihorac A, et al; Acute Disease Quality Initiative Workgroup 16. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13(4):241-257. doi:10.1038/nrneph.2017.2
78. Murugan R, Wen X, Keener C, et al; Biological Markers of Recovery for the Kidney (BioMaRK) Study Investigators. Associations between intensity of RRT, inflammatory mediators, and outcomes. *Clin J Am Soc Nephrol*. 2015;10(6):926-933. doi:10.2215/CJN.04560514

#### SUPPLEMENT.

**eTable 1.** ADQI 23 Working Groups and Assignments

**eTable 2.** Selected Articles that Served as Evidence for the Recommendations

**eTable 3.** GRADE System Used for Consensus Statement Ratings

**eFigure 1.** Kidney Health Assessment

**eFigure 2.** Use of AKI Biomarkers During Course of AKI