Overview of Diagnostic Criteria and Epidemiology of Acute Kidney Injury and Acute Kidney Disease in the Critically Ill Patient

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Abstract

Since the description *ischuria renalis* by William Heberden (1), AKI has remained a prominent complication of critical illness. Beyond KRT, treatment has been limited by the capacity to phenotype this condition. Here, we chronicle the evolution of attempts to classify AKI, including the adoption of consensus definitions, the expansion of diagnosis and prognosis with novel biomarkers, and emerging tools such as artificial intelligence (AI).

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The Need for a Consensus Definition

Classic textbooks characterize AKI as a rapid decline in GFR and retention of nitrogenous waste products (2). Although clinically accurate, lack of specificity has spawned >30 definitions, hindering comparisons between settings (3,4). To address these limitations, the Risk, Injury, Failure, Loss, and End Stage Renal Disease (RIFLE) scheme (Figure 1), initially proposed by the Acute Dialysis Quality Initiative (ADQI) in 2004, provided a standardized framework to classify AKI. The least severe category "risk" was defined as a 50% increase in serum creatinine or >25% decrease in eGFR presumed to have occurred within 7 days, with increases in severity labeled "injury," "failure," "loss," and "ESRD" with parallel criteria for oliguria (5). The subsequent Acute Kidney Injury Network (AKIN) Classification System in 2005 eliminated RIFLE's Loss and ESRD stages and eGFR criteria, and added KRT to stage 3 (6). Given studies showing mortality associated with small increases in creatinine (7), AKIN included a 0.3 mg/dl creatinine increase over 48 hours to improve sensitivity. The most recent AKI classification scheme, introduced by the Kidney Disease Improving Global Outcomes (KDIGO) workgroup in 2012 (8), combined elements of both: stage 1 AKI criteria could be met by an increase in creatinine of either 0.3 mg/dl within 48 hours or a 50% increase within 7 days with comparisons showing equivalent or superior sensitivity for AKI detection and similar prognostic performance for AKI staging and outcomes (9–12). Validation studies have also shown that the urine output criteria alone (13,14) and in combination with serum creatinine is associated with mortality in critically ill patients (15). Direct comparisons of urine output and creatinine criteria suggest that creatinine may be the more predictive of the two, with studies in cardiac surgery and cardiac intensive care unit (ICU) patients demonstrating higher risk for adverse outcomes (prolonged length of stay, KRT, and mortality) with AKI by creatinine criteria compared with equivalent stage AKI by urine output (16,17). AKI by both creatinine and urine output criteria had even higher risk of KRT and prolonged length of stay compared with AKI by creatinine alone (16). Despite the prognostic value of urine output, logistic and interpretative challenges have hindered its greater application and generalizability. The hourly capture of this information is challenging in patients without a catheter and outside the ICU and can be confounded by diuretic use and solute loading. Additionally, the optimal threshold urine output is unclear, with one study of patients undergoing abdominal surgery finding a risk of AKI associated with an intraoperative urine output <0.3 ml/kg per hour, but not with urine output <0.5 ml/kg per hour (18). Although routine surveillance may be challenging, short-term monitoring of urine output with provocative testing has shown promise as a prognostic marker in milder AKI. The "furosemide stress test," assessed by urine flow rate after a standardized dose of furosemide, has been shown to predict progression to higher stages of AKI (19,20).

What Have the Consensus Definitions Taught Us about AKI in the ICU

The application of these definitions uncovered the unappreciated burden of kidney dysfunction among the critically ill. Before RIFLE, reported incidences of AKI ranged from 1% to 25%, although these studies primarily focused on more severe AKI (3,4,21). Studies utilizing the RIFLE, AKIN, or KDIGO criteria in ICU populations reported higher incidences, with one- to two-thirds of patients afflicted (11,22–27). Consensus definitions have also elucidated the prognosis of AKI beyond earlier studies, which demonstrated in-hospital mortality rates of up to 40%–60% in severe cases (3,4). By leveraging a consistent framework, studies have shown that mild AKI is associated with mortality (7,28) and a graded association between

Stage	RIFLE	AKIN	KDIGO
Stage 1/ Risk	SCr 1.5x baseline (within 7 days) **or** GFR decrease >25%	SCr 1.5–2.0x baseline (within 7 days) **or** ≥0.3 mg/dl increase (within 48 h)	SCr 1.5–1.9x baseline (within 7 days) **or** ≥0.3 mg/dl increase (within 48 h)
Urine Output <0.5 ml/kg/h x 6 h			
Stage 2/ Injury	SCr 2x baseline **or** GFR decrease >50%	SCr 2–3x baseline	SCr 2.0–2.9x baseline
Urine Output <0.5 ml/kg/h x 12 h			
Stage 3/ Failure	SCr 3x baseline **or** GFR decrease 75% **or** Cr ≥4 (*with acute rise ≥0.5 mg/dl*)	SCr >3x baseline **or** SCr ≥4 (*with acute rise ≥0.5 mg/dl*) **or** initiation of KRT	SCr 3x baseline **or** increase in Cr ≥4 *(with ≥0.3 mg/dl increase within 48 h or 1.5x baseline)* **or** initiation of KRT
Urine Output <0.3 ml/kg/h x 24 h **or** anuria x 12 h			
Loss	Complete loss of kidney function >4 weeks		
ESRD	End-stage kidney disease (>3 months)		

Figure 1. | RIFLE, AKIN, and KDIGO systems for AKI classification. Urine output and serum creatinine criteria for the RIFLE, AKIN, and KDIGO classification systems for AKI. AKIN, Acute Kidney Injury Network; Cr, creatinine; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Assessment, Failure, Loss, and End Stage Renal Disease; SCr, serum creatinine.

increasing AKI severity and death (Table 1) (22,23,27,29–34). The former demonstrated that even in the absence of overt failure, lesser degrees of kidney dysfunction were clinically relevant, facilitating widespread adoption of the term "acute kidney injury." Although not limited to critical illness, studies using these definitions have also shown associations between AKI and long-term sequelae including kidney disease progression (35,36), cardiovascular outcomes (37–39), and frailty (40) (Table 1).

These consensus definitions have also provided a framework to study the dynamic trajectory of AKI during critical illness and the importance of recovery. In one study, patients who recovered from AKI within 7 days and did not experience a relapse had 1-year survival >90% (41), whereas those who had a relapse of AKI after early recovery had a five-fold higher risk of death at 1 year. No recovery from AKI had the worst prognosis with approximately 40% survival at 1 year (41). The extent to which these associations are explained by a lack of kidney recovery itself versus the more severe underlying illness prompting nonrecovery is not clear; however, these findings parallel studies of AKI survivors in large health care databases demonstrating an association between the degree of recovery and the risk for mortality and CKD over longer durations (35,42).

Use in Clinical Trials and Practice

AKI management recommendations on the basis of stage have been proposed in the KDIGO practice guidelines (8) and the National Kidney Foundation AKI Core Curriculum (43); however, benefit in routine practice remains to be demonstrated. More recently, the KDIGO criteria have been applied to standardize and improve the reproducibility of clinical trials and enrich for patients more likely to benefit from interventions. Recent studies comparing early versus late initiation of dialysis used these criteria to identify more advanced stages of AKI to enrich for participants more likely to require dialysis (44–47). These criteria have also been increasingly applied as outcomes in studies of balanced crystalloid use (48,49) and trials evaluating "bundle" interventions for AKI prevention (50,51). As familiarity improves, standard use of these criteria may also help audiences interpret and compare the effect of interventions.

Limitations of Consensus Definitions

Despite improving understanding, conceptual and logistic limitations remain. AKI requires observed changes in creatinine, but the "baseline" creatinine to anchor that definition is often missing. For patients admitted with elevated creatinine, it can be unclear whether the dysfunction is chronic or acute. Various strategies are used to impute surrogate values, each with strengths and limitations (Table 2), and this variety has hindered effective comparisons when applying consensus definitions (5,52–54). Although modifications to introduce specificity and "reduce the need for a baseline" (*e.g.*, use of a 48-hour window) have been proposed, the potential for underestimating AKI incidence or severity remains (Table 2). Further, creatinine and urine

Table 1. Studies of AKI outcomes

Study and Publication Year	Study Design	Criteria	Sample Size	Mortality, Stage 1 (AKIN, KDIGO), or Risk (RIFLE) (95% CI)	Mortality, Stage 2 (AKIN, KDIGO), or Injury (RIFLE) (95% CI)	Mortality, Stage 3 (AKIN, KDIGO), or Failure (RIFLE) (95% CI)	Study Population	End Point	Summary of Findings
Mortality									
Ostermann and Chang (23)	Retrospective	RIFLE	41,972	IR 20.9%[a]	IR 45.6% [a]	IR 56.8%[a]			
Hoste *et al.* (25)	Retrospective	RIFLE	5383	IR 8.8%[a]	IR 11.4%[a]	IR 26.3%[a]			
Bagshaw *et al.*	Retrospective	RIFLE	120,123	IR 17.9%[a]	IR 27.7%[a]	IR 33.2%[a]			
Lopes *et al.*	Retrospective	RIFLE	182	IR 27.3%[a]	IR 28.6%[a]	IR 55.0%[a]			
Thakar *et al.* (29)	Retrospective	AKIN	325,395	OR 2.2 (2.17 to 2.30)[b]	OR 6.1 (5.74 to 6.44)[b]	OR 8.6 (8.07 to 9.15)[b]			
Nisula *et al.* (11)	Prospective	AKIN, KDIGO	2901	IR 29.3% (25.2 to 33.3)[b]	IR 34.1% (27.8 to 40.3)[b]	IR 39.0% (34.3 to 43.8)[b]			
Hoste *et al.* (27)	Prospective	KDIGO	1802	OR 1.7 (0.9 to 3.2)[b]	OR 3.0 (1.4 to 6.3)[b]	OR 6.9[a] (3.9 to 12.2)[b]			
Long-term outcomes									
Coca *et al.* 2012 (36)	Systematic review and meta-analysis	RIFLE, AKIN	1,455,418				Hospitalized and nonhospitalized patients with and without AKI	CKD, kidney failure, and death	AKI associated with higher risk of incident CKD (pooled aHR 8.8; 95% CI, 3.1 to 25.5), kidney failure (pooled aHR 3.1; 95% CI, 1.9 to 5.0), and mortality (pooled aHR 2.0; 95% CI, 1.3 to 3.1) Graded association with AKI severity and risk of CKD or kidney failure
Bansal *et al.* 2018 (38)	Retrospective	KDIGO	150,434 matched pairs				Hospitalized adult veterans with and without AKI	Incident heart failure within 2 yr postdischarge	AKI associated with higher risk of incident heart failure (HR 1.23; 95% CI, 1.19 to 1.27)
Go *et al.* 2018 (39)	Retrospective	KDIGO	146,941 (31,245 with AKI)				Hospitalized adults with and without AKI	Heart failure, acute coronary syndromes, peripheral arterial disease, ischemic stroke events (up to 1 yr postdischarge)	AKI associated with higher risk of composite outcome of hospitalization for heart failure and atherosclerotic events (aHR 1.18; 95% CI, 1.13 to 1.25)

Table 1. (Continued)

Study and Publication Year	Study Design	Criteria	Sample Size	Mortality, Stage 1 (AKIN, KDIGO), or Risk (RIFLE) (95% CI)	Mortality, Stage 2 (AKIN, KDIGO), or Injury (RIFLE) (95% CI)	Mortality, Stage 3 (AKIN, KDIGO), or Failure (RIFLE) (95% CI)	Study Population	End Point	Summary of Findings
									Composite outcome driven by excess risk of subsequent heart failure (aHR 1.44; 95% CI, 1.33 to 1.56) Association with subsequent atherosclerotic events was nonsignificant (aHR 1.05; 95% CI, 0.98 to 1.12)
Abdel-Kader *et al.* 2018 (40)	Secondary analysis of prospective cohort study	KDIGO	1317				Critically ill adults with respiratory failure and/or shock	Clinical frailty status at 3 and 12 mo postdischarge	In adjusted models, AKI stages 1, 2, and 3 associated with higher frailty scores at 3 mo (OR 1.92; 95% CI, 1.14 to 3.24; OR 2.40; 95% CI, 1.31 to 4.42; OR 4.41; 95% CI, 2.20 to 8.82, respectively) Similar association between AKI stage and frailty scores at 12 mo (OR 1.87; 95% CI, 1.11 to 3.14; OR 1.81; 95% CI, 0.94 to 3.48; OR 2.76; 95% CI, 1.34 to 5.66, respectively)

Table 1. (Continued)

Study and Publication Year	Study Design	Criteria	Sample Size	Mortality, Stage 1 (AKIN, KDIGO), or Risk (RIFLE) (95% CI)	Mortality, Stage 2 (AKIN, KDIGO), or Injury (RIFLE) (95% CI)	Mortality, Stage 3 (AKIN, KDIGO), or Failure (RIFLE) (95% CI)	Study Population	End Point	Summary of Findings
See *et al.* 2019 (115)	Systematic review and meta-analysis	RIFLE, AKIN, KDIGO, VARC, VARC-2	2,017,437				Hospitalized adults with and without AKI	New or progressive CKD, kidney failure, death	AKI was associated with higher risk of new or progressive CKD (HR 2.67; 95% CI, 1.99 to 3.58), kidney failure (HR 4.81; 95% CI, 3.04 to 7.62), and death (HR 1.80; 95% CI, 1.61 to 2.02)
Ikizler *et al.* 2021 (37)	Prospective observational multicenter	KDIGO	1538769 with AKI (+769 non-AKI matched)				Hospitalized adults with and without AKI	Incident CKD, CKD progression, heart failure events, major atherosclerotic cardiovascular events, all-cause mortality Mean follow-up 4.5 yr (±1.8 yr)	AKI associated with higher adjusted rates of incident CKD (aHR 3.98; 95% CI, 2.51 to 6.31), CKD progression (aHR 2.37; 95% CI, 1.28 to 4.39), heart failure events (aHR 1.68; 95% CI, 1.22 to 2.31), all-cause mortality (aHR 1.78; 95% CI, 1.24 to 2.56) Risks of heart failure events and mortality nonsignificant when accounting for degree of kidney function recovery and proteinuria at 3 mo

AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Assessment, Failure, Loss, and End Stage Renal Disease; 95% CI, 95% confidence interval; IR, incidence rate; OR, odds ratio; aHR, adjusted hazard ratio; HR, hazard ratio; VARC, Valve Academic Research Consortium; VARC-2, Valve Academic Research Consortium–2.
[a]Hospital mortality.
[b]90-d mortality rate.

Table 2. Techniques for addressing missing baseline creatinine and their potential strengths and limitations (54,116)

Baseline Creatinine	Potential Strengths	Potential Limitations
Admission creatinine	• Available in nearly all hospitalized patients (imputation not needed) • Less likely to be confounded by prolonged illness or hospitalization exposures compared with later values • Works well if admission kidney function "normal"	• May underestimate incidence of AKI: can miss community-acquired AKI unless it worsens • Can underestimate AKI severity (stage) and erroneously assign a higher mortality per observed stage
Inpatient nadir creatinine	• Available in nearly all hospitalized patients (imputation not needed) • More likely to detect community-acquired AKI that resolves • Normal values suggest preserved kidney function at baseline	• May overestimate incidence and severity of AKI due to factors that confound serum creatinine (*e.g.*, fluid overload or reduced generation of creatinine) • May erroneously assign a lower mortality per observed stage • May underestimate incidence and severity in patients with community-acquired AKI that does not resolve
Imputed creatinine using eGFR 75	• Improves generalizability by allowing inclusion of patients who might otherwise be excluded	• May overestimate AKI incidence, severity, and associated mortality depending on population, such as those with a higher prevalence of CKD • Can hinder accurate modeling by providing an estimate of kidney function distribution that is narrower than reality
Rolling 48-h or 7-d windows	• Enriches for acuity • May be able to detect multiple episodes in a hospitalization	• May miss or underestimate severity of community-acquired AKI or anchor to long-term kidney outcomes • May be difficult to stage accurately • May miss slowly evolving AKI
Preadmission baseline	• Most likely to represent premorbid kidney function	• Only available in select patients • CKD progression could be interpreted as AKI in some when sensitive definitions for AKI used or time horizon long • May be challenging to determine the true baseline in patients with multiple disparate values or who are frequently hospitalized

output can be confounded by changes in the volume of distribution, diuretic use, and altered creatinine production, which can threaten specificity and project an overly optimistic picture of recovery (55–58). One study of patients with ICU stays >5 days showed persistent decreases in serum creatinine in both AKI and non-AKI patients (59). These limitations may be most apparent when using the most sensitive definitions of AKI (*e.g.*, stage 1). Notably, the original RIFLE criteria acknowledged that these criteria may be overly sensitive in attempting to capture the larger population at "risk" for parenchymal injury; however, labeling mild changes as "injury" in subsequent iterations may have unintendedly masked this original sentiment. Many of these limitations, and some emerging concepts, were noted in the 2019 KDIGO controversies conference of AKI, including the need for subsequent definitions to include distinctions for AKI persistence, transience, and relapsing or recovered AKI, and the potential incorporation of kidney injury biomarkers (60).

Perhaps the most insidious limitation of the consensus definitions is the temptation to mistake the precision they add as a replacement that addresses the larger phenotyping barriers still limiting progress in developing novel therapeutics in AKI. From the application of existing care strategies to better aligning novel interventions to target populations, the need for a pragmatic and accurate way to classify the heterogeneity and pathophysiology underlying AKI remains a critical challenge.

Acute Kidney Disease

It has also been recognized that AKI and CKD are not discrete entities, but exist in a continuum, with short reversible changes identified as AKI and persistent or irreversible changes in kidney function identified as *de novo* or progressive CKD. Although current AKI and CKD definitions are useful constructs for studying epidemiology, their limitations include failure to recognize smaller or more subacute changes in kidney function that are associated with clinically relevant outcomes or account for the prognostic importance of kidney function trajectory after an AKI event. In practice, the absence of an inclusive definition may delay recognition and treatment of acute kidney disorders not meeting AKI or CKD criteria but with common risk factors and outcomes.

To address these gaps, the term "acute kidney disease" (AKD) was first proposed as part of the 2012 KDIGO AKI definition to better identify all kidney injury (biomarker positivity, including proteinuria) or functional derangements lasting <90 days. In this paradigm, AKI—by virtue of placing a greater emphasis on events occurring within a shorter time frame (48 hours to 7 days)—is a subset of

AKD. Given the heterogenous nature of AKD, an initial classification system and management recommendations were not included. Non-AKI AKD could have several clinical phenotypes in both inpatient and outpatient settings, including newly identified biomarker positivity (proteinuria or novel biomarkers) in the absence of changes in kidney function, newly identified abnormalities in kidney function in the absence of a reference value, and subacute changes in kidney function (not meeting temporal AKI criteria).

AKD has not been systematically studied, due in part to the recognition that the term could represent many different phenotypes. James *et al.* described the incidence and prognostic importance of AKD in a Canadian population-based cohort study that included both hospitalized and nonhospitalized patients and found that AKD without AKI was three times more prevalent than AKI (3.8% versus 1.5%) and associated with a higher risk of CKD, kidney failure, and mortality compared with patients with no kidney disease (61). Similar findings have been shown using UK and Danish cohorts (62,63).

In 2017 the ADQI proposed an alternative definition of AKD that included a classification system and enhanced integration within the current AKI framework (64). In this schema, AKI was identified by acute changes in kidney function occurring within a 7-day time frame, with persistent changes in kidney function lasting beyond 7 days labeled as AKD (Figure 2). AKD could then be classified according to AKI stage to better classify the extent of kidney recovery and its prognostic effect after AKI. Changes persisting beyond 90 days would be reclassified as CKD. Although potentially useful in the setting of critical illness, where kidney function is frequently measured and etiology and epidemiology are well studied, frequent assessment of kidney function is lacking in most studies, with the lack of electronic health record (EHR) interoperability in the United States representing one challenge for follow-up. The framework requires further validation and does not address subacute kidney injury (non-AKI AKD), which clearly has prognostic importance. The KDIGO AKD definition was recently revised to reflect differences between AKD without AKI and AKD with AKI, with staging on the basis of eGFR and albuminuria added in those with AKD and not AKI (65). As our understanding of kidney injury evolves, our definitions of AKI and AKD will likely evolve in parallel.

Novel Biomarkers of AKI

The above attempts have collectively underscored sensitivity and specificity limitations of serum creatinine and urine output, a point recently illustrated by a biopsy series of kidney damage where one-third of patients did not meet KDIGO AKI criteria (66). These limitations have generated interest in the development and validation of novel biomarkers that better reflect parenchymal injury and provide prognostic information. Novel markers have generally been characterized as indicating tubular "damage" or "stress," with the former including, but not limited to, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule–1 (KIM-1), IL-18, and L-type fatty acid binding protein (L-FABP), and the latter including tissue-inhibitor of metalloproteinases 2 (TIMP-2) and IGF-binding protein 7 (IGFBP7). Other candidate biomarkers, such as C-C motif chemokine ligand 14 (CCL14), dickkopf-related protein 3 (DKK3), and chitinase 3–like–1 gene product (YKL-40), have emerged as potentially promising predictors of postoperative AKI (67), AKI persistence (68), and AKI progression and hospital mortality (69). These have led to novel concepts such as "subclinical injury" and characterizing AKI by the presence of functional and/or structural damage (Figure 3) (70). The clinical importance of subclinical injury was demonstrated in a study of the French and European Outcome Registry in ICUs (FROG-ICU) and Adrenomedullin and Outcome in Severe Sepsis and Septic Shock-1 (AdrenOSS-1) cohorts of critically ill

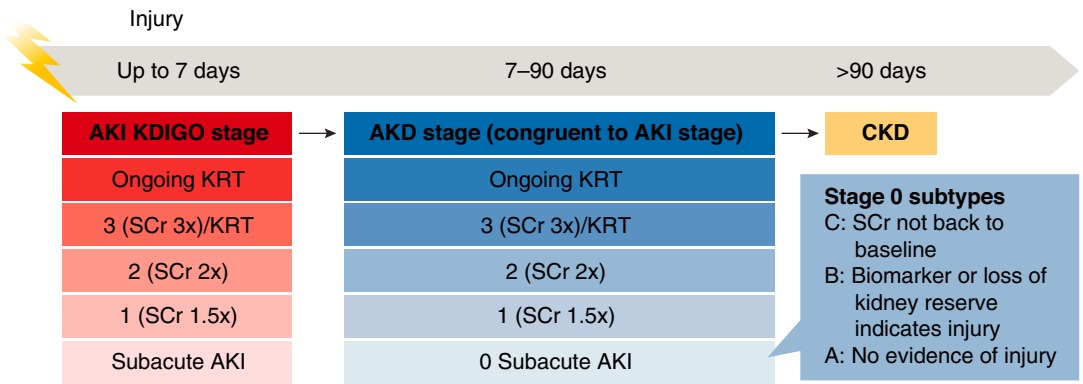

Figure 2. | AKI, acute kidney disease, and chronic kidney disease continuum. Framework proposed by the Acute Dialysis Quality Initiative (ADQI) workgroup for AKI, acute kidney disease (AKD), and CKD. Duration of time after the injury determines the category of disease (AKI, AKD, or CKD). Stages of AKD map to the corresponding AKI stages. Stage 0 AKD indicates partial recovery from AKI. Stage 0A includes patients who have completely recovered from AKI with no residual evidence of injury but retain the risk of long-term events. Stage 0B includes patients whose serum creatinine has returned to baseline but who have evidence of ongoing kidney damage, injury, or loss of kidney functional reserve. Stage 0C includes patients with serum creatinine levels above baseline but within 1.5 times baseline. Figure and caption from the consensus report of the ADQI 16 workgroup by Chawla *et al.* (64). KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine.

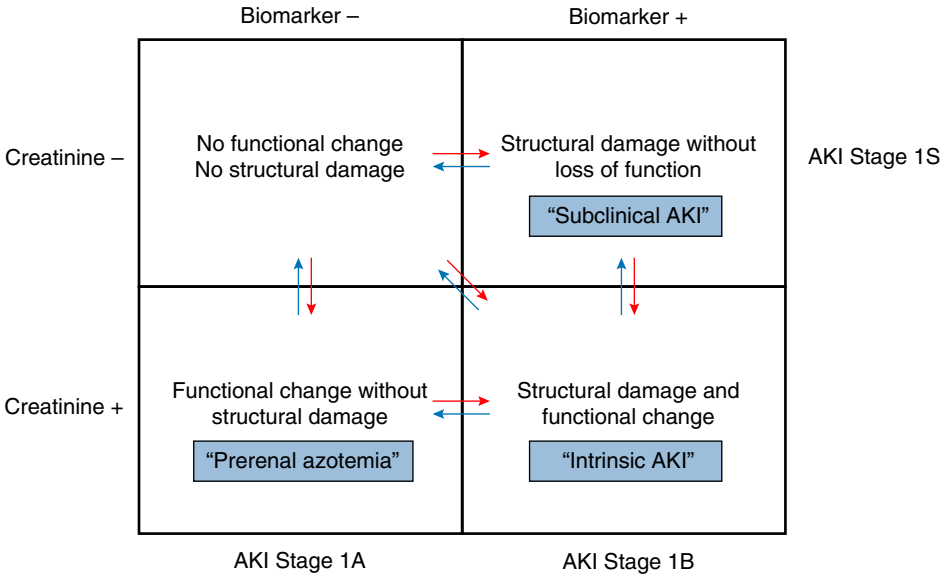

Figure 3. | **AKI categorization using novel biomarkers**. At the tenth consensus conference of the Acute Dialysis Quality Initiative (ADQI) workgroup, an early framework for the clinical use of novel biomarkers in combination with functional biomarkers of AKI (*i.e.,* serum creatinine and urine output) was developed, wherein functional change and evidence of structural damage (manifested by elevations in damage biomarkers) together provided more detailed categorization of AKI. This framework was recently updated during the 23rd ADQI meeting. In the revised system, each KDIGO stage of AKI is subcategorized by the presence or absence of damage biomarkers. For KDIGO stage 1 AKI (shown in the figure), these include stage 1S (*i.e.,* "subclinical" AKI), stage 1A (functional change without elevated damage biomarkers), and stage 1B (functional change and elevated damage biomarkers). Stages 2–3 AKI are defined by parallel criteria. These changes aim to improve the sensitivity for AKI detection and to discriminate underlying etiology and assess severity, although this staging system for AKI remains to be validated (91). Notably, subclinical AKI has been shown to be associated with adverse outcomes, including mortality and need for KRT (112,113). Red arrows denote progression; blue arrows denote resolution. Figure adapted from Koyner *et al.* (114) and Ostermann *et al.* (91). KDIGO, Kidney Disease Improving Global Outcomes.

patients, in which subclinical AKI (defined by elevated plasma proenkephalin A 119–159 levels) occurred in 6.1%–6.7% of patients and was associated with a higher risk of death at 28 days compared with those without subclinical AKI (hazard ratio [HR] 2.4; 95% confidence interval [95% CI], 1.5 to 3.7, for FROG-ICU cohort; HR 2.5; 95% CI, 1.1 to 5.9, for AdrenOSS-1 cohort) (71). Other areas of investigation have included risk stratification, early detection of AKI, assessing prognosis and recovery, enriching clinical trials, detecting nephrotoxic signals, and measuring responses to interventions.

A focus of early inquiry examined the potential of these markers to "predict" or detect early AKI, with studies demonstrating mixed performance (72–79). Two recently discovered markers, TIMP-2 and IGFBP7, are expressed in kidney tubular cells during physiologic stress or injury. Their combined use has been demonstrated to predict the development of stage 2–3 AKI within 12 hours in critically ill patients with areas under the curve between 0.79 and 0.82, generally outperforming earlier markers of tubular injury (80,81). Although the Food and Drug Administration allowed marketing as a complementary tool for risk assessment in adults with recent cardiovascular and respiratory failure (82), studies attempting to better define the clinical interpretation and actionability of TIMP-2*IGFBP7 and other markers remain. Some limitations include challenges with comparison with an imperfect creatinine standard (83–85) and difficulty pinpointing the exact timing of injury in the critically ill (86,87), which may help explain the superior negative predictive values relative to the more modest positive predictive values generally observed (88). Despite some uncertainty regarding their role for early diagnosis, several biomarkers have been shown to provide additional prognostic information (Table 3).

Notably, because kidney biopsies are rarely performed in the ICU, few studies have compared the performance of these markers against a histologic standard. One study examined the performance of L-FABP, IL-18, and KIM-1 for diagnosing acute tubular injury (ATI) on biopsy (89). Compared with serum creatinine, NGAL levels were higher in mild and severe ATI compared with no ATI and exhibited higher discrimination for severe ATI (0.67; 95% CI, 0.60 to 0.74) compared with creatinine alone (0.58; 95% CI, 0.49 to 0.67) (89). Although not in a critically ill population, these findings suggest that the specificity for some markers for detecting histologic ATI may be modest. Efforts to continue validating these markers and find clinicopathologic correlates are ongoing. One example is the Kidney Precision Medicine Project, an ambitious program whose goal is to prospectively enroll patients with AKI and CKD to define molecular pathways for specific disease subphenotypes through the collection of biospecimens and the development of a kidney tissue atlas (90).

Given these collective characteristics, the ADQI recently suggested that damage markers be combined with conventional functional markers to improve diagnostic accuracy and assess severity, including a modification to KDIGO staging that adds substages on the basis of biomarker levels

Table 3. Studies of novel biomarkers

Study and Publication	Biomarkers Studied	Sample Size	Study Design	Biomarker Inclusion Criteria	Patient Type at Time of Biomarker Measurement	Primary End Point	Summary of Findings
Clinical trials							
Endre *et al.* 2010 (117)	uGGT, uAP	162	Randomized double-blind placebo-controlled trial Evaluation of erythropoietin versus placebo to prevent AKI among critically ill adults	GGT×AP index ≥46.3		Relative average plasma creatinine increase from baseline over 4–7 d	No statistically significant difference in primary outcome or in AKI incidence between placebo and treatment groups (AKI incidence 48.7% in placebo group versus 48.8% in treatment group; $P>0.99$)
Zarbock *et al.* 2016 (45)	pNGAL	231	Randomized clinical trial, single center Evaluation of early versus delayed initiation of dialysis for AKI in critically ill adults with KDIGO stage 2 AKI	pNGAL >150 ng/ml		Mortality at 90 d	Reduced 90-d mortality in early initiation arm (39.3% versus 54.7%; HR 0.66; 95% CI, 0.45 to 0.97)
Meersch *et al.* 2017 (51)	TIMP-2*IGFBP7	276	Randomized controlled trial, single center Evaluation of KDIGO care bundle in patients with high risk of AKI after cardiac surgery	TIMP-2*IGFBP7 >0.3		AKI within 72 h of cardiac surgery	Reduced incidence of AKI in intervention arm (55% versus 71.7%; ARR 16.6%; 95% CI, 5.5 to 27.9)
Göcze *et al.* 2018 (50)	TIMP-2*IGFBP7	125	Randomized clinical trial, single center Evaluation of KDIGO care bundle in patients with high risk of AKI after major abdominal surgery	TIMP-2*IGFBP7 >0.3		AKI within 7 d of abdominal surgery	Nonsignificant reduction in AKI incidence in intervention arm (31.7% versus 47.5%; OR 1.96; 95% CI, 0.93 to 4.10) Significant reduction in AKI incidence in intervention arm in subgroup of

Table 3. (Continued)

Study and Publication	Biomarkers Studied	Sample Size	Study Design	Biomarker Inclusion Criteria	Patient Type at Time of Biomarker Measurement	Primary End Point	Summary of Findings
							patients with TIMP-2*IGFBP7 levels 0.3–2.0 (27.1% versus 48.0%; $P=0.03$)
Zarbock *et al.* 2021 (118)	TIMP-2*IGFBP7	278	Multicenter, multinational, randomized controlled trial Evaluation of adherence to KDIGO care bundle in patients with high risk of AKI after cardiac surgery	TIMP-2*IGFBP7 >0.3		Adherence to KDIGO bundle protocol	Higher rate of adherence to KDIGO bundle in intervention arm compared with control arm (65.4% versus 4.2%) Secondary end point: lower incidence of moderate and severe AKI in intervention group (14.0% versus 23.9%; ARR 10.0%; 95% CI, 0.9 to 19.1; $P=0.03$)
Prognosis							
Coca *et al.* 2014 (119)	uNGAL, uIL-18, uKIM-1, uL-FABP, urinary albumin	1199	Prospective observation, multicenter		Hospitalized adults after cardiac surgery (1–3 d post-op)	All-cause mortality (median follow-up 3 yr)	In patients with clinical AKI, highest tertiles of peak uNGAL, uIL-18, uKIM-1, uL-FABP, urinary albumin associated with 2- to 3.2-fold higher risk of mortality compared with lowest tertiles
Pike *et al.* 2015 (120)	IL-6, IL-8, IL-10, IL-18, MMIF, TNFR-I, TNFR-II, DR-5	817	Prospective, nested observational cohort, multicenter		Critically ill adults with AKI on KRT	Kidney recovery (alive and not on KRT by day 60 after hospital discharge), 60-d mortality	AUCs for kidney recovery: IL-6 0.61, IL-8 0.63, IL-18 0.58, MMIF 0.57 Clinical model AUCs for kidney recovery (0.73) and mortality (0.74). Addition of IL-8 to clinical model improved prediction of kidney recovery and mortality (0.76 and 0.78, respectively)

Table 3. (Continued)

Study and Publication	Biomarkers Studied	Sample Size	Study Design	Biomarker Inclusion Criteria	Patient Type at Time of Biomarker Measurement	Primary End Point	Summary of Findings
							IL-8 improved IDI and NRI for kidney recovery and mortality
Koyner *et al.* 2015 (121)	TIMP-2*IGFBP7	692	Secondary analysis of prospective observational multicenter		Critically ill adults at time of ICU admission	Composite outcome of all-cause mortality or need for KRT at 9 mo	Unadjusted analysis: TIMP-2*IGFBP7 >2.0 associated with higher risk of end point (HR 2.11; 95% CI, 1.37 to 3.23) Multivariable analysis: TIMP-2*IGFBP7 >0.3 associated with end point only in patients who developed AKI (HR 1.44; 95% CI, 1.00 to 2.06, for levels 0.3 to ≤2.0; HR 2.16; 95% CI, 1.32 to 3.53, for levels >2.0)
Parr *et al.* 2015 (122)	uL-FABP, uIL-18, uKIM-1, uNGAL	152	Prospective observational		Critically ill adults with stage 1 AKI	Composite outcome of persistent doubling of SCr (≥2 d), KRT, and mortality	AUCs for predicting composite outcome: uL-FABP 0.79, uIL-18 0.64, uKIM-1 0.62, uNGAL 0.65, combination of biomarkers 0.81 Clinical model AUC for composite outcome was 0.74; adding uL-FABP to clinical model improved AUC (0.82)
Hollinger *et al.* 2018 (123)	penkid	583	Prospective observational		Critically ill adults with sepsis or septic shock	MAKE at 7 d	penkid concentration on admission associated with MAKE (aOR 3.3; 95% CI, 1.8 to 6.0)
Xie *et al.* 2019 (124)	TIMP-2*IGFBP7	719	Prospective observational		Critically ill adults with and without AKI	In-ICU mortality and initiation of CRRT	Among patients with AKI, those with elevated TIMP-2*IGFBP7 levels

Table 3. (Continued)

Study and Publication	Biomarkers Studied	Sample Size	Study Design	Biomarker Inclusion Criteria	Patient Type at Time of Biomarker Measurement	Primary End Point	Summary of Findings
							had higher in-ICU mortality (OR 2.087; 95% CI, 1.241 to 3.510) and more frequently reached composite end point of in-ICU mortality or CRRT initiation (OR 2.290; 95% CI, 1.401 to 3.744)
Schunk *et al.* 2019 (67)	DKK3	733	Prospective observational		Adults undergoing elective cardiac surgery (DKK3 measured preoperatively)	AKI Secondary outcomes: persistent kidney dysfunction, KRT at 60 d	AUC for postoperative AKI 0.783 (95% CI, 0.747 to 0.20). Adding DKK3 to clinical prediction model improved IDI and NRI Elevated DKK3 (>471 pg/mg) was associated with higher risk of persistent reduction in eGFR during follow-up compared with those with DKK3 <471 pg/mg (OR 2.01; 95% CI, 1.26 to 3.21)
Legrand *et al.* 2019 (125)	Cys C, pNGAL, uNGAL, penkid	1207	Prospective observational, multicenter		Adult survivors of ICU who had received at least 24 h of mechanical ventilation or hemodynamic support Biomarkers measured at time of ICU discharge	All-cause mortality at 1 yr	Biomarker levels (Cys C, pNGAL, uNGAL, proenkephalin 119–159) all associated with increased all-cause mortality at 1 yr aOR for 1-yr mortality: uNGAL 2.08 (95% CI, 1.35 to 3.21); pNGAL 2.61 (95% CI, 1.71

Table 3. (Continued)

Study and Publication	Biomarkers Studied	Sample Size	Study Design	Biomarker Inclusion Criteria	Patient Type at Time of Biomarker Measurement	Primary End Point	Summary of Findings
							to 3.97); Cys C 3.11 (95% CI, 1.88 to 5.16); proenkephalin 119–159 2.20 (95% CI, 1.44 to 3.38)
Hoste *et al.* 2020 (126)	pNGAL, uNGAL, TIMP-2*IGFBP7, uCCL14, penkid, uCHI3LI, Cys C, uL-FABP, uKIM-1, GST-π, IL-18	331	Prospective observational, multicenter		Critically ill adults with stage 2–3 AKI (within 36 h of meeting KDIGO criteria)	Development of persistent severe AKI (KDIGO stage 3) for ≥72 h	uCCL14 was most predictive of persistent stage 3 AKI (AUC 0.83; 95% CI, 0.78 to 0.87)
Bagshaw *et al.* 2021 (68)	uCCL14	195	Secondary analysis of prospective observational multicenter		Critically ill adults within 36 h of onset of stage 2–3 AKI	Development of persistent severe AKI (KDIGO stage 3 for ≥72 h, or death or KRT occurring before 72 h)	AUC for uCCL14 0.81 (95% CI, 0.72 to 0.89) Risk of persistent severe AKI was higher with higher values of uCCL14 KRT and/or death at 90 d was higher within tertiles of uCCL14 concentration

uGGT, urinary γ-glutamyl transpeptidase; uAP, urinary alkaline phosphatase; GGT, gamma-glutamyl transpeptidasealkaline phosphatase; pNGAL, plasma neutrophil gelatinase–associated lipocalin; KDIGO, Kidney Disease Improving Global Outcomes; HR, hazard ratio; 95% CI, 95% confidence interval; TIMP-2, tissue inhibitor of metalloproteinases–2; IGFBP7, IGF-binding protein 7; ARR, absolute risk reduction; OR, odds ratio; uNGAL, urinary neutrophil gelatinase–associated lipocalin; uIL-18, urinary IL-8; uKIM-1, urinary kidney injury molecule–1; uL-FABP, urinary liver-type fatty acid–binding protein; IL-6, plasma IL-6; IL-8, plasma IL-8; IL-10, plasma IL-10; IL-18, plasma IL-18; MMIF, macrophage migration inhibitory factor; TNFR-I, TNF receptor 1; TNFR-II, TNF receptor II; DR-5, death receptor–5; AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification index; ICU, intensive care unit; SCr, serum creatinine; penkid, proenkephalin A 119–159; MAKE, major adverse kidney events (>50% increase in Cr from baseline, KRT, in-hospital death); aOR, adjusted odds ratio; CRRT, continuous renal replacement therapy; DKK3, dickkopf-3; Cys C, plasma cystatin C; uCCL14, urinary C-C motif chemokine ligand 14; uCHI3LI, urinary chitinase-3–like protein 1; GST-π, glutathione S-transferase–π.

(91). The overall strength of the recommendation was a B (conditional), indicating that further research is needed to improve confidence. Nevertheless, many of these markers have been leveraged in recent clinical trials to enrich for populations at higher risk for clinical outcomes (Table 3) (45,50,51). In the Biomarker Guided Implementation of the KDIGO Guidelines to Reduce the Occurrence of AKI in Patients After Cardiac Surgery (PrevAKI) study, an AKI care bundle (optimization of volume status and hemodynamics, avoidance of nephrotoxins, and prevention of hyperglycemia) was tested in patients undergoing cardiac surgery among those with an elevated level of TIMP-2*IGFBP7 ($\geq$0.3) after cardiopulmonary bypass and demonstrated reduced incidence of AKI (Table 3) (51). Similarly, the Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery (BigpAK) study tested an AKI bundle in patients undergoing major abdominal surgery and used TIMP-2*IGFBP7 levels to identify ICU patients at high risk of AKI. Although no global differences in AKI stages between arms were observed, a subgroup with elevated biomarker levels showed a reduction in AKI incidence (27% versus 48%; $P=0.03$) (50). These studies indicate that biomarker-guided interventions may be useful in identifying patients who may respond to clinical interventions. Whether these performance characteristics can extend to routine practice for triage purposes, or prompt more aggressive diagnostic evaluation or resuscitation, is under investigation (92,93).

Another interest has been in determining whether biomarkers can discriminate between known phenotypes of AKI and help discover new phenotypes. Few studies have compared expression patterns of biomarkers to differentiate causes of AKI. In one study of 218 patients who underwent kidney biopsies for evaluation of AKD, high levels of TNF-α and IL-19 were strongly associated with acute interstitial nephritis, enhancing the area under receiver operating characteristic curve of prebiopsy clinical impression (94). Recently, a substudy of the Vasopressin and Septic Shock Trial in patients with AKI measured angiopoietin-1 and -2, soluble tumor necrosis factors receptor 1, and IL-18 and used latent class analysis to identify two subphenotypes of AKI, one of which had a higher risk of nonrecovery and 28-day mortality, suggesting that similar approaches could be used to identify molecularly distinct AKI subphenotypes with differential responses to therapy (95).

In summary, novel biomarkers for AKI remain an evolving area of investigation. Despite ongoing molecular and clinical validation of their strength as specific indicators of tubular injury or stress, findings to date have led to early applications suggesting potential use cases in clinical trials, in phenotyping, and in guiding current clinical management.

Artificial Intelligence/Informatics

The simplicity of laboratory-based consensus definitions of AKI makes them an ideal target for interventions using clinical decision support (CDS). Leveraging EHRs using bioinformatics and AI has potential uses in the context of AKI, including AKI alerting, predictive analytics, AKI phenotyping, and risk-based management. The feasibility of CDS/AI to reduce the rate, duration, and intensity of AKI has been demonstrated in a number of clinical settings (96,97). Not all studies using CDS/AI have demonstrated improved outcomes (98) however, perhaps reflecting differences in implementation and clinical heterogeneity.

Predicting AKI using CDS paired with specific interventions may be more promising. The Nephrotoxic Injury Negated by Just in time Action (NINJA) alert program is a notable example, where Goldstein and colleagues demonstrated a sustained reduction in nephrotoxin-mediated AKI in hospitalized pediatric patients by identifying patients at highest risk through nephrotoxic drug exposure and deprescription (99). The NINJA alert program has been validated in multiple centers (100).

AI has been used to predict AKI in numerous care settings (101–103). Koyner *et al.* utilized EHR data to develop a prediction tool that predicts stage 2 AKI a median of 41 hours before a rise in serum creatinine and the need for dialysis within 2 days. The tool performed well across numerous adult care settings (102). Siminov *et al.* implemented an AKI prediction tool across several institutions and were able to predict AKI 24 hours before a rise in creatinine and the need for dialysis and mortality (103). Other groups have used similar techniques to predict AKI in specific clinical settings, including adults with severe burns (104), and acute pancreatitis (105), postoperative (106), and cardiac patients (107,108). Although such prediction tools have potential to mitigate ongoing kidney injury, all require external validation and their implementation has not been shown to improve patient-centered outcomes. Evidence-based interventions supported by these risk-prediction tools need to be tested before widespread implementation.

AI may have a further role in phenotyping AKI trajectory and risk assessment after an AKI event, including prediction of risk of rehospitalization, recurrent AKI, heart failure hospitalization, and other comorbidities. Semler *et al.* demonstrated the feasibility of using AI to predict major adverse kidney events by 30 days (MAKE 30), which may allow delivery of risk-stratified post-AKI follow-up care in the future (109).

There are many opportunities to leverage the power of AI to recognize and phenotype AKI and to improve the care and follow-up of AKI patients. The AI working group of the AKI!Now initiative of the American Society of Nephrology represents the growing momentum in this field and ongoing collaborative efforts to use data science and quality initiatives to improve early recognition and treatment of AKI and to reduce the disease burden on patients and health systems (110,111).

Conclusion

Critically ill patients are subject to diverse and severe forms of AKI. Although the past three decades have brought significant advances in AKI epidemiology and prognosis, the development of treatment for AKI beyond supportive (*i.e.,* dialytic) therapy has been stalled by the limited phenotyping of this heterogeneous condition. There is reason for optimism, however, because continued multifaceted approaches to advance AKI phenotyping may

eventually allow investigators to better pair potential therapies with underlying pathophysiology and identify new targets.

Disclosures

N. Pannu reports employment with Alberta Health Services; consultancy agreements with GE; serving on the board of directors of the Kidney Foundation of Canada, Northern Alberta branch; and funding from Amgen for a quality improvement initiative in ESKD. N. Pannu also reports honoraria from Astellas in 2011; World Congress of Nephrology (WCN)—covered travel expenses as speaker $1000.00 in 2013; International Society of Nephrology (ISN)—covered travel expenses of $700.00 for Mexican National Nephrology Meeting March 2015; Acute Dialysis Quality Initiative (ADQI)—travel expenses for November 2015, June 2017 meeting; WCN—speaker, covered expenses 2017, 2019, 2020; and ISN—speaker, covered expenses 2017, 2018, 2019, ADQI AKI meeting 2020 $1000.00 USD honorarium, and AKI Continuous Renal Replacement Therapy meeting 2021 (provided microphone and lamp for speakers). E.D. Siew reports employment with Nashville Veterans Affairs, consultancy agreements with Akebia Therapeutics on 4/2019, honorarium for an invited educational talk on AKI epidemiology at the DaVita Annual Physician Leadership Conference 2/2019, serving as an Associate Editor of *CJASN*, and royalties as an author for UpToDate. The remaining author has nothing to disclose.

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Author Contributions

Bethany C. Birkelo was responsible for conceptualization, data curation, methodology, and visualization; wrote the original draft; and reviewed and edited the manuscript. Neesh Pannu was responsible for conceptualization, data curation, investigation, methodology, and visualization; wrote the original draft; and reviewed and edited the manuscript. Edward D. Siew was responsible for conceptualization, investigation, methodology, project administration, supervision, and visualization; wrote the original draft; and reviewed and edited the manuscript.

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