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Authors
Kwong, Yuenting D
Liu, Kathleen D

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AKI Adjudication: Do We Need It?

Yuenting D. Kwong[a], **Kathleen D. Liu**[a,b]

[a]Division of Nephrology, Department of Medicine, University of California, San Francisco, CA, USA

[b]Critical Care Medicine, Department of Anesthesia, University of California, San Francisco, CA, USA

Abstract

Adjudication, which comes from the Latin term “adjudicare” (to act as a judge), uses expert opinion to define and classify disease entities. The use of clinical adjudication may help to define more homogeneous disease subsets but comes at the expense of effort needed and generalizability. Here, we will describe the pros and cons of acute kidney injury (AKI) adjudication under varied circumstances. We will use heart failure as a paradigm and provide comparable examples from the current AKI literature.

Keywords

Acute renal failure; Disease categories; Heart failure

In the current era, acute kidney injury (AKI) is typically defined using consensus criteria such as the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [1]. Due to the strong association of AKI with adverse outcomes, AKI is defined by modest alterations in serum creatinine or urine output. However, these AKI definitions based on consensus criteria describe a heterogeneous disease – for example, acute interstitial nephritis and acute tubular necrosis (ATN) are 2 separate pathophysiological entities, but may be considered one disease using consensus criteria. Here, we will describe the pros and cons of AKI adjudication under varied circumstances. We will use heart failure as a paradigm and provide comparable examples from the current AKI literature.

First, it is perhaps the easiest to define when adjudication is not needed. Adjudication is often unnecessary for large epidemiological studies, where the intent is to describe the association of broadly defined disease with specified outcomes. For example, in a landmark study, Chertow et al. [2] described the association of small changes (e.g., a 0.3 mg/dL increase) in serum creatinine with mortality and hospital length of stay. Since the focus of this analysis was on hospital-acquired AKI and its relationship with adverse outcomes, adjudication of the outcome would not have changed the findings per se.

Dr. Kathleen D. Liu, Division of Nephrology, Department of Medicine, University of California, San Francisco, Box 0532, San Francisco, CA 94143-0532 (USA), Kathleen.Liu@ucsf.edu.

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With regard to heart failure, event ascertainment as well as staging and management algorithms all currently require some form of clinical classification. In particular, expert opinion was used to create criteria for defining heart failure events, as obtaining an echocardiogram or right heart catheterization in every patient during a potential heart failure exacerbation is not feasible, and agreement with regards to the presence or absence of heart failure is critical for robust clinical research studies. Consequently, heart failure is typically defined by the presence of 2 major or 1 major and 2 minor criteria (Table 1) [3]. These criteria are relatively sensitive and adequately specific for the diagnosis of heart failure and can be abstracted from the medical record [4]. The staging of heart failure is based on New York Heart Association classification scheme based on clinical symptoms [5] and associates with patient prognosis. The American College of Cardiology/American Heart Association classification scheme for chronic heart failure ties clinical stages to actionable management [6]. With the advancement and increasing availability of echocardiogram, subtypes of heart failure (e.g., dilated, restrictive vs. hypertrophic) have further guided the management of the disease.

In the field of AKI, consensus criteria have been proposed to define AKI severity based on urine output and changes in serum creatinine [1]. Since AKI, unlike heart failure, is asymptomatic until its most advanced stages, objective clinical and laboratory criteria rather than symptom-based criteria are needed to define severity (Table 2). Similar to heart failure, more severe AKI is associated with poorer short- and long-term outcomes, including chronic kidney disease, end-stage renal disease, and death. However, AKI as currently defined is also a heterogeneous disease, and AKI studies aiming to more thoroughly study the pathophysiology, prognosis, and outcomes of AKI subsets have been limited by our inability to define homogeneous disease subsets. Not only is it not feasible to obtain a renal biopsy on every patient with AKI, it is also unknown if these tissue samples would even allow us to classify disease adequately.

For AKI event ascertainment, clinical adjudication by expert opinion may be superior to the use of KDIGO staging alone. The 2 approaches have been compared to diagnosis based on consensus criteria alone in a biomarker registration trial [7]. IGFBP7*TIMP2 is the only biomarker with FDA clearance to identify patients at high risk of AKI over the next 12 h [8]. For the IGFBP7*TIMP2 registration study, 3 nephrologists independently reviewed clinical data to determine whether AKI was present or absent. Standardized elements of the clinical history were abstracted for review. Importantly, as part of this process, the 3 adjudicators reviewed and discussed a series of training cases, and case report forms were refined based on the adjudicator discussion. Agreement among adjudicators was higher for non-AKI than for AKI cases (97.3 vs. 78.9%). Agreement between adjudicators (defined by the majority opinion) and KDIGO criteria was similarly higher for non-AKI than AKI cases (97.9 vs. 91.5%). With regards to biomarker levels, there was a dose-response curve between the number of experts who felt that a subject had AKI and biomarker levels. Finally, when those who had adjudicated AKI (defined by the majority opinion), but not KDIGO AKI, were compared to those who had KDIGO AKI, but not adjudicated AKI, biomarker levels were higher in those with adjudicated AKI. Thus, for studies of the association of biomarkers with AKI, adjudicated AKI appears to be a preferable outcome to the use of AKI defined based on creatinine or urine output alone.

However, if criteria to define disease subtypes are not clearly present or definable, adjudication can pose major challenges. This is highlighted by a biomarker study from TRIBE-AKI, a cohort of patients undergoing coronary artery bypass grafting [9]. Three nephrologists were asked to determine if patients had prerenal azotemia or ATN. Full consensus was achieved only for 19% of cases, and there was significant variation between adjudicators. While one adjudicator considered 13.4% of the cases to be pre-renal azotemia and 73.2% of the cases to be ATN, another adjudicator considered 58.2% of cases to be prerenal azotemia and 58.2% to be ATN (with the rest indeterminate). Consequently, differences between biomarker levels in these diseases were modest at best. Thus, for studies that focus on AKI subtypes, standardized criteria for disease adjudication should be considered, and at present, it is harder to adjudicate disease subtypes than the presence/absence of disease. In the future, biomarkers may help better define some of these disease subtypes.

Finally, with regards to treatment, treatment for AKI is currently supportive, but similar to the American College f Cardiology/American Heart Association classification chronic heart failure, the KDIGO AKI guidelines [1] propose some supportive care for AKI based on disease stage. In the future, these treatment decisions will likely incorporate both disease subtype and severity.

In sum, analogous to other diseases, there is an important role for adjudication of disease events as well as subtypes in the field of AKI. In the future, the field of AKI may advance through the development of classification schemes similar to those used for heart failure. Development, refinement, and testing of consensus criteria for scheme for adjudication are critical next steps.

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Table 1.

Clinical criteria for heart failure [3]

Major criteria
Paroxysmal nocturnal dyspnea
Neck vein distension
Rales
Radiographic cardiomegaly
Acute pulmonary edema
Third heart sound
Central venous pressure >16 cm H_2O
Circulation time ≥25 s
Hepatojugular reflex
Weight loss ≥4.5 kg in 5 days in response to treatment
Minor criteria
Bilateral ankle edema
Nocturnal cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion decrease in vital capacity by 33%
Tachycardia (rate ≥120 beats/min)

In all cases, criteria cannot be attributable to other diagnoses (e.g., pneumonia leading to dyspnea or pleural effusion).

Table 2.

Classification systems for heart failure (HF) and AKI

Purpose of classification	Congestive HF	AKI
Diagnosis (event)	Framingham criteria (Table 1)	KDIGO criteria (urine output and/or serum creatinine often applied but adjudication may be preferable
Severity	New York Heart Association (clinical symptoms)	KDIGO criteria (urine output and/or serum creatinine)
Treatment decisions	American College of Cardiology/American Heart Association (at risk, asymptomatic, clinical HF, refractory HF)	Decisions proposed based on KDIGO criteria in AKI guidelines, but limited evidence base
Subtype	Echocardiography	To be determined: Imaging? Biomarkers?