Risk Stratification for Acute Kidney Injury: Are Biomarkers Enough?

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Acute kidney injury (AKI) is a common and serious complication that is associated with several adverse outcomes in hospitalized patients. AKI significantly increases the risk of mortality, need for renal replacement therapy, and intensive care admission, and it also has serious economic ramifications. Effective risk stratification to identify patients at risk for severe AKI is essential for targeting our health care and research resources to tackle this important public health issue. The overwhelming majority of research in earlier diagnosis and risk stratification of AKI over the past 10 years has focused on novel biomarker development. The purpose of this review is to provide an update on other novel risk stratification tools than can be used in the prognostication of AKI. We discuss the utility of the furosemide stress test in predicting the severity of AKI and the renal angina index in predicting the occurrence of AKI. We also discuss NephroCheck, a prognostic test that measures tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for the early detection of severe AKI.

Key Words: Acute kidney injury, Risk assessment, Biomarkers, Renal replacement therapy

INTRODUCTION

Acute Kidney Injury (AKI): Risk Factors, Risk Stratification Scores, and Kidney-Specific Severity Scores

We have made significant advancement in medicine since the term "risk factor" was first introduced over half a century ago to predict disease occurrence and outcomes.[1] Many risk prediction models and methods are incorporated to assist clinicians in their decision-making process when managing patients with many medical diseases. AKI is an exception to this rule where risk prediction models and stratification scores are rarely used in real time to predict which patients are at high risk. Instead, the development of functional and damage biomarkers over the last 10 years has dramatically improved risk stratification for the identification of AKI and to enrich the target population for interventions in AKI clinical trials. Although the true potential of AKI biomarkers is still being appreciated, in September 2014, the US Food and Drug Administration allowed marketing of NephroCheck. This prognostic test, which measures urinary levels of tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor–binding protein 7 (IGFBP7), was approved to detect early severe AKI starting a new era of AKI care and biomarker utilization.[2]

Before discussing existing and novel methods for assessing risk, it is worthwhile to examine selected fundamental concepts in the risk stratification of AKI. Importantly, the use of the term "AKI" in this article is most consistently linked with the clinical and histologic diagnosis of acute tubular injury. We have intentionally omitted a discussion of biomarkers and prediction risk tools to assist in the differential diagnosis of AKI. Although there are ample data to suggest that biomarkers of AKI can distinguish across AKI subtypes, a discussion around this is beyond the scope of this review.[3-6] Second, AKI is a complex syndrome, and the risk of AKI is the result of multiple interactions and factors that result in a continuous spectrum of risk. Even mild forms of AKI can impact short- and long-term morbidity and mortality.[7-10] Specific treatments for AKI are lacking, and supportive care is the mainstay of therapy rendering the prevention of AKI paramount. Currently, the inability to rapidly diagnose AKI with the present-day standard serum creatinine has been one of the obstacles to developing effective therapeutics to diminish kidney damage in the immediate aftermath of an inciting insult.[11] Despite the prevalence and impact of risk stratification scores in cardiovascular disease and other systems, there are only a few externally validated scoring tools for the different pathophysiological processes established in AKI. Many established risk factors may help identify some risk for development of AKI but do not convey most of the risk. Similarly, patients considered at low risk for development of AKI may have a higher risk of mortality when compared with high-risk patients with respiratory or cardiovascular failures.[12] Currently available risk scores to predict AKI are often not sensitive or specific enough to identify high-risk individuals and poorly predict AKI progression.[13-15] Possible explanations for this include the inability to account for patient heterogeneity in the setting of critical illness,[16] difficulty reproducing results in larger patient cohort studies,[16,17] and a failure to calculate these complex scores at the bedside. Many, but not all, of these risk scores require further refinement and validation; and as a result, many of these scores have failed to translate into current clinical practice. Despite this, understanding an

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individual's AKI risk profile may in reality offer the opportunity for prevention or early intervention. Patients in the intensive care unit (ICU) are at particular risk, more specifically those undergoing mechanical ventilation,[18,19] receiving vasoactive medication and those with sepsis,[20,21] preexisting CKD, and exposure to nephrotoxins or cardiopulmonary bypass.[22-25] Other established risk factors are advanced age,[26] obesity,[26-28] hypoalbuminemia,[28,29] hyperuricemia,[28,30] chronic heart disease,[31] chronic liver disease/hepatic failure,[32] diabetes, volume overload,[19,33] and prior episodes of AKI.[19,28,31]

AKI risk prediction scores[17,24,25,34-42] and kidney-specific scoring models[10,13,15,17,43-45] are 2 risk models that have been developed in patients without AKI and those with established AKI, respectively. These scoring systems are very similar in that they rely on common clinical and biochemical parameters, but distinct differences exist between the 2 scoring systems. AKI risk prediction scores use risk factors to assess the probability of developing AKI and/or the need for renal replacement therapy (RRT) in patients without preexisting kidney dysfunction, whereas kidney-specific severity scores are used to analyze the effect of comorbidities on mortality in patients with established AKI.

Several risk prediction models have been developed and validated in the setting of cardiac surgery when the exact timing of an inciting kidney insult is known.[24,34,35] Since 1997, at least 8 prediction models have been developed to identify those patients at risk for cardiac surgery–associated AKI, and these are highlighted in Table 1.[25,34,36-42,46] The prediction models highlighted in Table 1 differ in the patient risk factors used, AKI outcome definitions with some scores focusing exclusively on the need for postoperative RRT.[34,46] A key drawback of these risk scores is their limitation in predicting milder forms of AKI.[35,47] One study by Kiers, performed a head-to-head comparison of these 8 prediction models in cardiac surgery–associated AKI defined by RIFLE criteria and need for dialysis in 1388 consecutive adult cardiac surgery patients.[34] The prediction model with the highest discriminative power to identify those individuals at risk of developing severe postoperative AKI requiring RRT was the Cleveland Clinic scoring tool, area under the curve (AUC; 95% confidence interval [CI]) of 0.93 (0.91-0.94).[34,37] The discriminative value to predict postoperative RRT by the Cleveland Clinic scoring system was further corroborated in another single-center retrospective cohort of 12,096 patients undergoing cardiac surgery.[46]

In contrast to prediction scores, kidney-specific severity scores have been used to analyze the effect of comorbidities on mortality in patients with already established kidney failure. These AKI-specific severity scores incorporate physiological, organ dysfunction, laboratory, and previous comorbidity to predict mortality. Examples of these scoring systems include: Bullock,[15] Lohr,[44] Liano,[13] Mehta,[17] Chertow,[10,14] Paganini,[43] SHARF II,[48] and Demirjian[45] and are highlighted in Table 2. The scoring models are complex, and they poorly predict AKI, AKI progression, and mortality (as shown by low AUC-receiver operating characteristics).[16] Many of the scoring models used randomly elevated creatinine cutoff levels in the definition of AKI and also failed to incorporate the use of RRT in the scores. Importantly, none of these scores have gained widespread acceptance with several of these systems being limited in that they were conducted in a single center, whereas others failed to be externally validated.

Another area of AKI where risk stratification scores have gained popularity is the area of contrast-induced acute kidney injury (CI-AKI). Numerous risk score models have been proposed to predict patients at risk for CI-AKI.[54-56] One score that has excellent discriminatory capacity for predicting CI-AKI in patients with acute coronary syndrome who underwent coronary angiography is the Mehran risk score.[54] The Mehran risk score uses patient-related characteristics and procedure-related characteristics, such as use of intra-aortic balloon pump or increasing volumes of contrast media. Increasing score number confers exponentially increased CI-AKI risk. The Mehran risk score for CI-AKI continues to be validated in several studies many years after its publication.[57]

The Beginning and Ending Supportive Therapy (BEST) Kidney Investigators externally validated 4 AKI severity scores prospectively in 1700 critically ill patients across 54 centers.[16] All scores had low AUROCs (Mehta AUC (95% CI) 0.67 (0.64-0.70), Liano 0.70 (0.67-0.72), Chertow 0.61 (0.58-0.63), and Pagnini 0.64 (0.61-0.67)) for the prediction of inpatient mortality in patients with AKI.[16] In another large multicenter epidemiologic study, the UK Intensive Care National Audit and Research Center Case Mix Program used 17,326 AKI patients to externally validate 3 AKI scores and also showed low AUCs (SHARF 0.63 [0.62-0.64], SHARF II 0.67 [0.66-0.68], and Mehta 0.69 [0.68-0.70]).[58] Ohnuma and colleagues used the Japanese Society for Physicians and Trainees in Intensive Care database which included 343 patients with AKI who required continuous renal replacement therapy (CRRT) in 14 ICUs.[59] The AUC curves revealed low discrimination ability of several of the AKI severity scores (Mehta 0.65 [0.59-0.71], SHARF II 0.64 [0.58-

CLINICAL SUMMARY

- Serum creatinine and urinary output have inherent limitations in the early diagnosis of AKI.
- Improved AKI risk stratification techniques need to be developed as they may be used to better inform timing decisions for RRT initiation and AKI therapeutics.
- Several AKI risk prediction scores and kidney-specific scoring models have been developed and validated in the setting of cardiac surgery; however most of these scores fail to predict milder forms of AKI.
- Many novel AKI risk assessment techniques have been developed over the past 5-10 years including Renal Angina Index, functional and damage biomarkers, and the Furosemide Stress Test; however these methods still require large scale validation.