

Commentary on Biomarkers for Early Detection and Prognosis of AKI

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Overview

Malhotra and Siew provide a detailed and highly comprehensive review of the AKI literature that carefully delineates the major categories of AKI biomarker studies. These studies can be broadly classified as addressing questions pertaining to screening or “early detection,” prognosis, and pathogenesis of human kidney injury. The authors organize the blood and urinary AKI biomarkers according to their presumed mechanisms as representing filtration, tubular function, tubular injury, or cell cycle arrest. The major findings are listed below.

- (1) The vast majority of studies of early detection and prognosis were performed among critically ill or postoperative patients. Among these populations, AKI biomarkers provide more precise ascertainment of the timing of renal injury and are associated with a higher incidence of clinical AKI. However, results of these studies may not be generalizable to other patient populations at risk for AKI.
- (2) The optimal timing of biomarker measurements and the use of serial repeated measurements remains uncertain. Generally, the accuracy for early AKI detection is greatest for AKI events that occur shortly after biomarker measurements. Some studies suggest that measuring change in these biomarkers may offer greater accuracy than measurements at a single point in time.
- (3) Most studies have demonstrated that AKI biomarkers provide moderate discrimination for the early detection of AKI. In general, the negative predictive values of AKI biomarkers are much greater than the positive predictive values, suggesting potential use in identifying patients who will not develop clinical AKI. However, predictive values are highly dependent on the incidence of AKI.
- (4) Limitations in the standard clinical definition of AKI (based on serial changes in serum creatinine and urine output) may affect the measured accuracy of the biomarkers. If mild cases of true renal tubular injury (e.g., as determined through histopathology) are mischaracterized *via* standard clinical definitions of AKI, then the accuracy of biomarkers in detecting true renal injury may be underestimated.
- (5) Some studies among patients who have established AKI report moderate discrimination of biomarkers

for renal recovery. Improved discrimination of biomarkers in this area could provide a potential strategy for planning of long-term RRT among AKI patients.

Evaluating Screening and Prognostic Studies

Studies of screening or “early diagnosis” of AKI seek to evaluate whether urine and serum biomarkers can predict the future development of AKI, as detected by standard clinical practice (e.g., increase in serum creatinine levels, decrease in urine output) among patients who do not have clinically apparent AKI at the time of testing. An important justification for any screening test is that treatment of early disease detected by screening must be more effective than treatment of late disease identified by clinical measures. However, at present, no interventions have been shown to more effectively prevent AKI or reduce the severity of this condition when detected at an earlier stage by biomarkers. Such interventions would need to target kidney injury within a narrow time window, because AKI typically manifests clinically within 24–48 hours following biologic injury to the kidneys. The lack of actionable interventions for patients who have high or low values of AKI biomarkers limits the clinical application of screening for this condition at present.

Prognosis studies of AKI seek to test whether urine and serum biomarkers can predict clinical outcomes, such as survival or renal recovery, among patients who already have established AKI. Although proven therapies are not yet available to reduce the duration of AKI or to prevent disease complications, risk stratification of AKI patients has potential clinical utility for counseling and long-term planning. However, at the present time, biomarker tests lack sufficient validity to materially impact clinical decision-making. For example, consider a typical marker, for which high serum levels are associated with a three-fold greater risk of death or dialysis dependence at 90 days among critically ill patients who have moderate to severe AKI (Table 1).

The overall 90-day incidence of mortality or dialysis dependence in this cohort of critically ill AKI patients is 300 of 1000 (30%) in the absence of testing. If an AKI patient is found to have a high level of the new marker, then their 90-day incidence of death or dialysis dependence would be 100 of 200 (50%). On the other hand, if an AKI patient is found to have a normal or low level of

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Table 1. Association of hypothetical serum marker with mortality or dialysis dependence

Serum Marker Level	Mortality or Dialysis Dependence (<i>n</i> =300)	Survival Free of Dialysis (<i>n</i> =700)	Total
High	100	100	200
Normal or low	200	600	800

Relative risk: $(100/200)/(200/800)=3.0$.

the marker, then their 90-day incidence of mortality or dialysis dependence would be 200 of 800 (25%). These differences may not be clinically significant in terms of their impact on patient or family counseling or planning for long-term RRT. Moreover, clinical characteristics, such as comorbid conditions and the severity of illness, may have similar or even greater impact on these probabilities. The evaluation of screening and prognosis studies should focus on these material effects of testing on patient care and outcomes, rather than statistical methods for evaluating these tests (*e.g.*, reclassification indices), because such statistical metrics do not address the basic question of whether testing is clinically helpful.

Perhaps the most direct application of current AKI biomarker studies is to advance understanding of the major underlying mechanisms of human kidney injury. Studies demonstrat-

ing that changes in levels of neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, insulin-like growth factor binding protein 7, tissue inhibitor of metalloproteinases-2, and other molecules prior to the clinical onset of AKI are critical for identifying mechanistic pathways of AKI, and are essential for developing effective future therapeutic interventions.

Disclosures

None.

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See related article, "Biomarkers for the Early Detection and Prognosis of Acute Kidney Injury" on pages 149–173.