Kidney360

Towards a Better Crystal Ball: Urinary C-C Motif Chemokine Ligand 14 (CCL14) and Persistent Severe AKI

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KIDNEY360 3: 1124–1127, 2022. doi: https://doi.org/10.34067/KID.0002162022

AKI is a common complication among hospitalized patients, occurring in up to 25% of admissions and in >50% of patients admitted to intensive care units (ICUs) (1). Depending on the etiology and extenuating clinical factors, AKI may resolve spontaneously or be readily responsive to appropriately applied interventions such as volume resuscitation or discontinuation of nephrotoxic drugs. Those patients with persistent AKI, however, have been shown to be at increased risk of both short- and long-term adverse outcomes, including in-hospital (2) and long-term mortality (3–5) and increased incident and progressive CKD (5,6).

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines were published, which included recommended strategies for forestalling AKI in high-risk patients (7). These recommendations, often colloquially known as the KDIGO bundle, include avoiding nephrotoxins, optimizing volume status, close hemodynamic monitoring, daily measurements of serum creatinine, monitoring of urine output, avoidance of hyperglycemia, and avoiding or minimize intravenous iodinated contrast agents. Although not explicitly recommended as a means by which recovery from extant AKI can be hastened, adhering to these strategies is widely considered best clinical practice regardless of AKI etiology. Unfortunately, the complexities of clinical practice often preclude adherence to the full set of guidelines, and several studies have demonstrated variable and suboptimal compliance (8,9). If objective tests were available to ascertain which patients are at greatest risk of persistent AKI, clinicians could better weight the risks and benefits of, for example, continuing a potentially nephrotoxic but clinically effective antibiotic or pushing additional necessary volume expansion in a patient at risk for respiratory complications (10). The value of predicting which patients with AKI will experience relatively rapid recovery versus those destined for progressive or persistent disease has only increased after multiple recent studies have shown no benefit in early initiation of RRT in the acute setting. The STandard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury trial randomized patients either to begin RRT within 12 hours of meeting clinical eligibility criteria or to defer it unless urgent clinical criteria were met or the AKI persisted for at least 72 hours (11). Although there was no difference in 90-day mortality, the delayed initiation patients had less dependence on RRT at 90 days and a lower peri-trial adverse event rate. The majority (though not all [12]) of comparable trials have noted similar findings (13,14). If there is no benefit to early RRT and clear potential harm and increased costs in delivering unnecessary RRT to patients destined to recover, then the necessity of objectively demarcating whether AKI will rapidly recover versus persist takes on even greater urgency.

The quest for objective tests related to the early detection, differential diagnosis, and clinical prognosis of AKI has driven an explosion of interest in novel kidney biomarkers over the past 20 years (15–17). Of these potential roles for biomarkers, predicting prognosis has been less studied and has usually entailed investigating the association of biomarkers with death or transition to or progression of CKD (18). Despite the well-recognized association between AKI duration and adverse outcomes, few studies have evaluated the ability of biomarkers to predict persistence of AKI (19). The RUBY study was a multicenter, international, prospective observational study attempting to identify biomarkers predictive of the durability of KDIGO-defined AKI stage 3 in patients admitted to an ICU with stage 2 or 3 AKI (20). Of multiple measured biomarkers, the most predictive of persistent stage 3 AKI was urinary C-C motif chemokine ligand 14 (CCL14), with an area under the receiver operating curve (AUC) of 0.83 (95% confidence interval [CI], 0.78 to 0.87). In this metric, CCL14 performed better than several frequently investigated biomarkers, including urinary neutrophil gelatinase-associated lipocalin, liver fatty acid binding protein, IL-18, tissue inhibitor of metalloproteinases-2, IGF-binding protein 7, kidney injury molecule-1, and plasma cystatin C. The performance of CCL14, however, was not statistically different from that of serum creatinine at the time of enrollment (AUC=0.81; 95% CI, 0.76 to 0.86, P=0.63). The association between CCL14 and AKI persistence has since been replicated in two additional studies with comparable predictive performance (21,22).

In this issue of *Kidney360*, Koyner *et al*. have conducted an analysis of the RUBY study, attempting to

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identify specific biomarker cutoff values of CCL14 for predicting persistence of severe AKI. Persistent severe AKI was defined as maintaining KDIGO stage 3 AKI for at least 72 hours. As part of a composite primary outcome, patients receiving RRT or those who died before 72 hours while still in stage 3 AKI were considered to have reached the end point of persistent AKI. The investigators sought to establish two distinct cutoffs for risk assessment: one at a lower CCL14 concentration to ensure high sensitivity to facilitate identifying the majority of patients who would develop persistent severe AKI, and a second higher cutoff with high specificity to identify those patients who should be aggressively prioritized to receive measures recommended by the KDIGO Clinical Practice Guidelines. These cutoffs were determined by optimizing the operating characteristics of sensitivity, specificity, and negative and positive predictive values. A low cutoff value for urinary CCL14 of 1.3 ng/ml was met by 211/335 (63%) patients and provided a high sensitivity (91%; 95% CI, 84% to 96%) in identifying patients who developed persistent severe AKI with a negative predictive value of 92%. A high cutoff of 13 ng/ml was met by 54/335 (16%) patients and achieved high specificity (93%; 95% CI, 89% to 96%) with a positive predictive value of 72% (negative predictive value of 75%). In multivariable adjusted analyses, with a CCL14 concentration ≤1.3 ng/ml as the reference, a concentration between 1.3 and 13 ng/mL had an adjusted odds ratio of 3.82 (95% CI, 1.73 to 9.12; $P=0.001$) for the development of persistent severe AKI, whereas a CCL14 >13 ng/ml had an adjusted odds ratio of 10.4 (3.89–29.9; $P<0.001$). Assessing the individual components of the composite end point at 5 days, RRT and persistence of stage 3 AKI increased significantly across CCL14 strata, whereas there was no significant difference in death. However, at 90-day follow-up, higher CCL14 levels at enrollment were significantly associated with an increased risk for both RRT and death. CCL14 was also measured in 378 health subjects and 366 patients with chronic, stable comorbidities, with each groups' median value being significantly less than 1.3 ng/ml.

Were novel biomarkers to spring forth in a biomedical vacuum, demonstration of their prognostic ability/association with clinical outcomes would be sufficient to recommend their clinical use. Of course, in workaday medical practice, multiple clinicals variables already exist with demonstrated utility for differential diagnosis and prognosis. For a new biomarker to be worthy of recommendation for clinical uptake, it must be demonstrated to expand upon or go beyond currently available clinical variables and models. In the RUBY study, patients who developed persistent stage 3 AKI had a lower body mass index and were less likely to have a history of diabetes mellitus but had higher enrollment serum creatinine values and KDIGO AKI stage, steeper creatinine trajectory (change in serum creatinine over the day before enrollment), and greater nonrenal Acute Physiology, Age, Chronic Health Evaluation (APACHE) III scores at enrollment compared with patients who did not develop persistent AKI. Interestingly, there was no difference in mechanical ventilation or use of vasoconstrictors between the two groups. Enrollment creatinine, KDIGO stage, and nonrenal APACHE III scores also increased significantly across strata of CCL14. As creatinine itself seems to be a strong predictor of persistent AKI, the question must be asked as to whether CCL14 improves existing clinical prognostic tools or whether it is simply a marker of the severity of AKI and general degree of illness already demonstratable by a higher serum creatinine.

Despite this valid concern, there are several considerations that suggest CCL14 may, in fact, expand prognostic ability regarding persistence of AKI beyond existing clinical variables. Importantly, CCL14 remained significantly associated with the primary outcome even when adjusted for enrollment creatinine, creatinine trajectory, and AKI stage. In a model containing the above three creatinine variables, body mass index, nonrenal APACHE III, and diabetes status, CCL14 in both strata >1.3 ng/ml maintained a higher odds ratio for the primary outcome than any of the creatinine variables (author correspondence). Addition of CCL14 to the model on the basis of existing clinical variables increased the AUC by a small but statistically significant value (0.86 [95% CI, 0.82 to 0.9]) to 0.88 [95% CI 0.85 to 0.92]). The authors also assessed the prognostic performance of urine output in the 24 hours before enrollment, given its known association with AKI recovery (23). The predictive performance of CCL14 was markedly stronger (AUC=0.82 [95% CI, 0.77 to 0.87] versus 0.63 [95% CI, 0.57 to 0.7]), and urine output was not significantly associated with the primary outcome in multivariate analysis.

The median baseline creatinine in the RUBY study for both those who would and those would not ultimately have persistent severe AKI was 1 mg/dl. At enrollment, creatinine was significantly lower in those who would not have persistent severe AKI (2.1 mg/dl [interquartile range (IQR), 1.5–2.8, with a median of 2.1]) than in those who would (3.4 mg/dl [IQR, 2.6–4.2, with a median of 3.4], $P<0.001$). As stage 3 AKI requires at least a 200% increase in creatinine from baseline and a 200% increase from a baseline of 1 mg/dl implies a creatinine >3 mg/dl, it is, on one level, a mathematical tautology that patients in stage 3 AKI at enrollment were more likely to still be in stage 3 at 72 hours. However, etiologies of AKI, especially in the ICU, exist across a spectrum from functional to structural. In patients with structural AKI, recovery depends in part on the delicate balance between injury/inflammation and repair played by recruited monocytes and macrophages. The ability to assess a patient's status on the spectrum from injury to repair would add welcome granularity to clinical prognostication beyond simply the severity of AKI. Given this, there is biologic plausibility to CCL14's potential as an independent predictor of AKI persistence. CCL14 is a chemokine that has been demonstrated to play a role in monocyte/macrophage recruitment and is associated with proinflammatory chemotaxis in multiple diseases, including lupus erythematous, rheumatoid arthritis, and multiple sclerosis (24,25). CCL14 is not expressed in mice or rats, and thus preclinical data related to AKI are very limited. It has been proposed that CCL14, released from injured tubular epithelial cells, stimulates the differentiation of monocytes to macrophages and T-cell differentiation into proinflammatory type 1 helper (T_H1) cells (26). As a marker potentially mechanistically tethered to propagation of structural injury, CCL14 seems well positioned for synergistic prognostication when paired with creatinine, a marker of glomerular filtration.

This is an important study in a field (AKI biomarkers) long festooned with promise but with little clinical payoff in the form of available, objective, cutoff-defined assays. The study has several strengths. CCL14 was measured in a diverse, mixed-unit patient population utilizing a standardized assay that (unlike the vast majority of investigated biomarkers) can be run on an established, clinically available, real-time testing platform (NEPHROCLEAR) (27). CCL14 maintained an independent association with hard clinical outcomes despite adjustment for a robust set of existing clinical variables, demonstrating the ability to add novel, additive information to clinical decision making. The study is not, however, without limitations. Biomarkers, including CCL14, were only measured at one time point in the RUBY study. Once specific cutoffs are introduced, it can be difficult to interpret what are sure to be dynamic tests, with values rising and falling above the cutoffs due to both the passage of time and potential layering of additional insults. In addition, it has not yet been demonstrated that identifying those patients at greatest risk for persistent AKI does, in fact, improve hard outcomes *via* alterations in clinical interventions such as volume management, medication changes, or RRT initiation. Nevertheless, the data presented in this issue of *Kidney360* are impressive findings and an important step forward in biomarker development. Future interventional trials with CCL14 levels affecting clinical decision making will be required to determine the precise role of this novel marker in the management of patients with AKI (28).

Disclosures

J.M. Belcher reports consultancy for Chiasma Pharmaceuticals and Mallinckrodt Pharmaceuticals; honoraria from Chiasma Pharmaceuticals and Mallinckrodt Pharmaceuticals; and an advisory or leadership role for Mallinckrodt Pharmaceuticals.

Funding

None.

Acknowledgments

The content of this article reflects the personal experience and views of the author and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the author.

Author Contributions

J. Belcher wrote the original draft of the manuscript and reviewed and edited the manuscript.

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Received: June 6, 2022 **Accepted:** June 8, 2022

See related article, "Performance of a Standardized Clinical Assay for Urinary C–C Motif Chemokine Ligand 14 (CCL14) for Persistent Severe Acute Kidney Injury," on pages 1158–1168.