All that glitters may not be gold: Changes in serum creatinine may not be the criterion standard for acute kidney injury

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Disclosures: R.C.A. has an unrestricted educational grant from Pfizer Canada Inc and has received honoraria from Mallinckrodt Pharmaceuticals for work unrelated to this article. N.T. has nothing to disclose with regard to commercial support.

Received for publication Jan 15, 2018; accepted for publication Jan 26, 2018; available ahead of print March 9, 2018.

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J Thorac Cardiovasc Surg 2018;155:2439-40

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2018.01.047>

Navdeep Tangri, MD, PhD, FRCPC (left), and Rakesh C. Arora, MD, PhD, FRCSC (right).

Central Message

Studies showing that acute kidney injury (subclinical or clinical) is treatable, and that successful treatment prevents long-term chronic kidney disease or death, are needed to move the field forward.

See Article page 2441.

Acute kidney injury (AKI) after cardiac surgery is common and associated with multiple adverse short- and long-term outcomes. In surgical and nonsurgical settings, AKI is typically defined by urinary output, or more commonly serum creatinine, based criteria, and physicians use changes in serum creatinine to follow its progression. Serum creatinine is only a filtration marker, however, and it may not necessarily reflect changes in tubular structure of function. In the case of chronic kidney disease, this is well recognized, and albuminuria is considered an equally important component of the chronic kidney disease staging system.

In this issue of the *Journal*, Albert and colleagues¹ have provided a single-center subanalysis from a multicenter randomized, controlled trial (Sodium Bicarbonate in Cardiac Surgery Study [Bi-NC]; total N = 350 patients) of adult cardiac surgical patients at increased risk for AKI. Specifically, they have endeavored to demonstrate the limitations of perioperative clinical serum creatinine-based definitions of AKI. Albert and colleagues¹ studied 200 participants and divided them into AKI status according to biomarker positivity and RIFLE criteria (risk, injury, failure, loss of kidney function, and end-stage kidney disease) positivity. As expected, they found that patients who were biomarker negative and RIFLE negative had the lowest risk of adverse outcomes. They also identified an important subgroup (biomarker positive and RIFLE negative), however, that was larger than the RIFLE-positive population and was consistently and strongly associated with renal replacement therapy, in-hospital mortality, and long-term outcomes. The findings were strongest for neutrophil gelatinase-associated lipocalin but were also positive for midkine, interleukin 6, and proteinuria and were negative for C-reactive protein. On the basis of these results, Albert and colleagues¹ concluded that patients with the subclinical AKI phenotype (biomarker positive

and RIFLE negative) should be considered a high-risk group and that the current creatinine-based definitions have key limitations.

Strengths of the study include its prospective follow-up and its inclusion of short- and long-term outcomes. Several limitations, however, must also be recognized. These include a limited number of outcomes (only 4 kidney failure events) and a limited number of deaths, restricting the statistical power and therefore suggesting cautious interpretation of the multivariable models. In addition, there were multiple biomarkers and multiple outcomes, all of which can lead to false-positive findings and require appropriate statistical correction. External validation of these findings in larger, multicenter cohort studies is therefore critically needed.

Nonetheless, the findings from this study question the current dogma of using serum creatinine as the “criterion standard” and clinical biomarker of choice for management of cardiac surgery-associated AKI. This study and others make it abundantly clear that relying on creatinine (a late injury filtration marker) alone does ignore subclinical tubular injury, which is associated with adverse short- and long-term outcomes. Incorporation of these markers could result in a new AKI staging system, which includes a 2 × 2 grid that incorporates tubular markers on one axis and creatinine-based criteria on the other. Ultimately,

studies that demonstrate that AKI (subclinical or clinical) is treatable, and that successful treatment prevents long-term chronic kidney disease or death, are really needed to move the field forward.

Reference

1. Albert C, Albert A, Kube J, Bellomo R, Wettersten N, Kuppe H, et al. Urinary biomarkers may provide prognostic information for subclinical acute kidney injury after cardiac surgery. *J Thorac Cardiovasc Surg*. 2018;155:2441-52.e13.