Letters

Urinary Hyaluronic Acid as an Early Predictor of Acute Kidney Injury After Cardiac Surgery

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequent, complex clinical problem in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). CSA-AKI is an important predictor of morbidity and mortality after cardiac surgery (1).

Changes in serum creatinine level and/or urine output, as proposed in the current consensus criteria (2), do not allow for the diagnosis of CSA-AKI until 24 to 48 h after surgery (3). Although treatment options for AKI are still limited, prevention of further damage as early as possible and timely prognostication are crucial to improve outcomes.

Newer biomarkers exist (e.g., urinary interleukin-18, urinary NGAL, or urinary KIM-1), but the performance of these markers to predict CSA-AKI is not optimal. Hyaluronic acid (HA) is a crucial, structural component of the extracellular matrix in many organs, including the kidneys. A broad spectrum of HA-mediated cell and organ function make HA a highly interesting target with respect to AKI (4). Here, we tested whether urinary HA (uHA) concentration can predict CSA-AKI earlier than currently used clinical parameters. We studied patients at high risk for CSA-AKI, as identified by a Cleveland Clinic Score ≥6; this score is composed of 13 pre-operative risk factors, including patient characteristics, comorbidities, and type of surgery (5). Our primary endpoint was the development of CSA-AKI, as defined by the KDIGO criteria (2).

Fifty patients with a Cleveland Clinic Score ≥6 were included in our study, and 26 (52%) of these patients developed AKI. Patients who did not develop CSA-AKI did not have a significant increase in uHA concentration post-operatively (all p > 0.05). In contrast, patients who developed CSA-AKI had a strong, significant increase in uHA concentration as early as 4 h after surgery and lasting until 24 h after surgery (compared with pre-CPB, all p ≤ 0.05)

(Fig. 1A). These results remained unchanged when the uHA concentration was normalized for urinary creatinine concentration; only the time profile of the point estimates for the uHA shifted slightly (Fig. 1B).
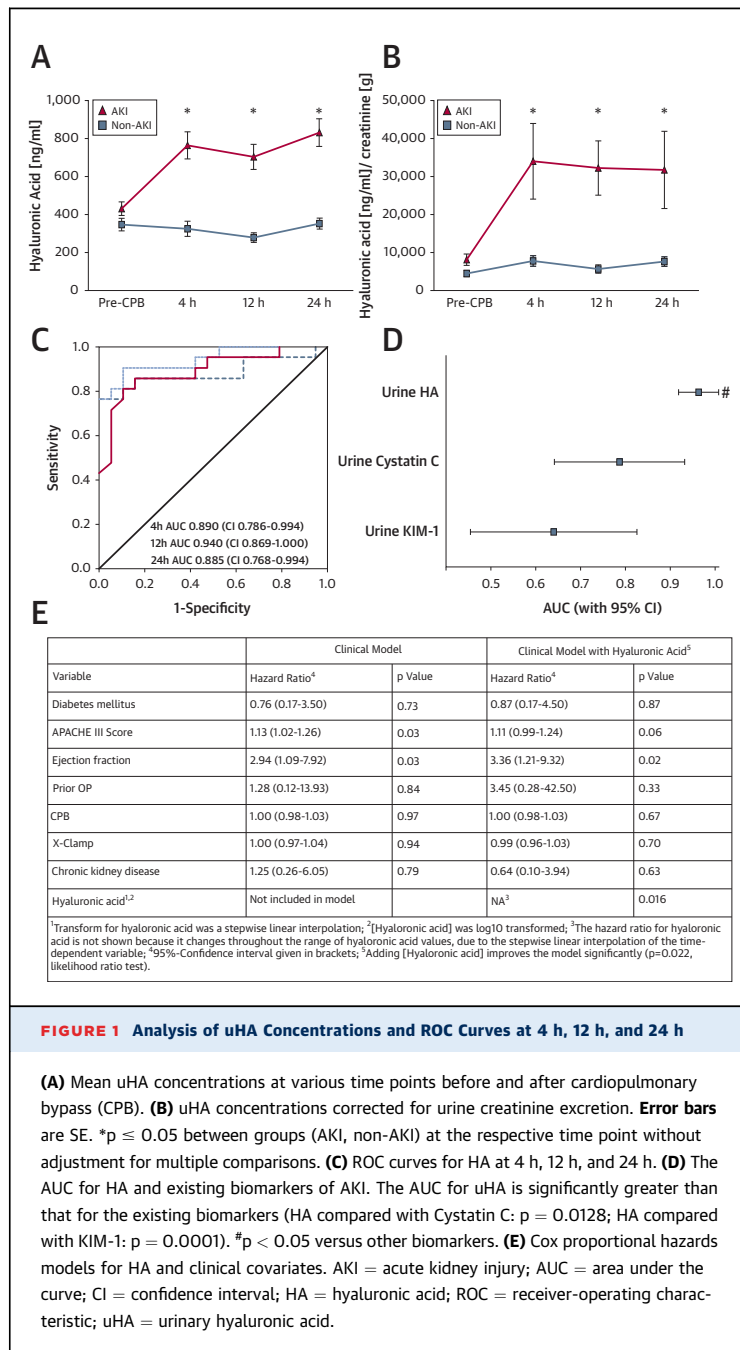
Renal HA expression is increased in some chronic disease states, such as diabetes and nephrolithiasis, which in turn have the potential to lead to chronic renal insufficiency (4). Moreover, both diabetes and pre-operative renal insufficiency increase the risk of CSA-AKI (5). In our study population, baseline uHA concentrations were not elevated in patients with diabetes or pre-operative renal insufficiency, suggesting that uHA concentration can serve as a marker of AKI. The cause of elevated uHA concentrations during AKI remains unknown at this time.

To examine whether uHA can predict CSA-AKI, we calculated receiver-operating characteristics and their respective area under the curve (AUC). For uHA, the AUC was 0.89 (95% confidence interval [CI]: 0.79 to 0.99), 0.94 (95% CI: 0.87 to 1.00), and 0.89 (95% CI: 0.77 to 0.99) at 4 h, 12 h, and 24 h after CPB, respectively (Fig. 1C). The AUC for uHA was significantly greater than that for the 2 existing biomarkers, suggesting better diagnostic performance of uHA. Patients with a uHA concentration >400 ng/ml at 12 h after surgery had a 6.8-fold higher risk of CSA-AKI than those with a uHA concentration <400 ng/ml.

When added to a 7-parameter clinical model, uHA significantly improved risk prediction for our primary endpoint (Fig. 1E). uHA remained strongly associated with AKI in this model.

To our knowledge, this is the first study describing uHA as an early predictive biomarker of CSA-AKI. We showed that uHA concentrations increase as early as 4 h after CPB in those who later develop CSA-AKI, whereas uHA concentrations remain unchanged in patients who do not develop AKI. An AUC >0.9 suggests better performance than other new biomarkers. In addition, uHA showed excellent performance despite heterogeneous comorbidities in our patient population, which is a strength of our study. Pre-existing renal insufficiency did not affect baseline uHA concentrations.

Our study has several limitations that do not allow us to generalize the findings. Most importantly, we studied only a small number of patients at high risk

FIGURE 1   Analysis of uHA Concentrations and ROC Curves at 4 h, 12 h, and 24 h

(A) Mean uHA concentrations at various time points before and after cardiopulmonary bypass (CPB). **(B)** uHA concentrations corrected for urine creatinine excretion. **Error bars** are SE. *p ≤ 0.05 between groups (AKI, non-AKI) at the respective time point without adjustment for multiple comparisons. **(C)** ROC curves for HA at 4 h, 12 h, and 24 h. **(D)** The AUC for HA and existing biomarkers of AKI. The AUC for uHA is significantly greater than that for the existing biomarkers (HA compared with Cystatin C: p = 0.0128; HA compared with KIM-1: p = 0.0001). #p < 0.05 versus other biomarkers. **(E)** Cox proportional hazards models for HA and clinical covariates. AKI = acute kidney injury; AUC = area under the curve; CI = confidence interval; HA = hyaluronic acid; ROC = receiver-operating characteristic; uHA = urinary hyaluronic acid.

for CSA-AKI at one institution. Our results require validation in larger multicenter studies.

In summary, our preliminary study indicates that uHA has the potential to become a highly useful biomarker for early prediction of CSA-AKI.

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Would a Modified Lewis Index Be More Specific, Without Marked Reduction of Sensitivity, in ECG Diagnosis of RVH?

Whitman et al. (1) should be congratulated for their important contribution on the electrocardiogram (ECG) diagnosis of right ventricular hypertrophy (RVH). The authors' database comprised 3,719 patients with normal left ventricular morphology and function who had an ECG and a cardiac magnetic resonance imaging-based assessment for RVH and were free of clinical cardiac disease, although some patients had hypertension, diabetes, or hypercholesterolemia. The authors implemented 22 ECG diagnostic criteria (Table 1 in their paper) and found that "a total of 6% had RVH, which was generally mild," and that the "ECG criteria were specific (many >95%) but had low sensitivity…The positive predictive values were not sufficiently high as to be