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Title: THE UTILITY OF BIOMARKER EXCRETION RATES IN ACUTE KIDNEY INJURY (AKI)

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INTRODUCTION AND AIMS: The urinary concentration of an AKI biomarker depends on the concentrating ability of the kidney. To account for inter-individual variation, many studies index biomarkers to urine creatinine under the assumption that urine creatinine concentration reflects water reabsorption. However, tubular secretion of creatinine increases this concentration independently of water reabsorption. Measurement of excretion rates is an alternative method of accounting for variability in water reabsorption. We compared urine concentration, excretion rate, and indexed biomarker concentration (biomarker divided by creatinine concentration) in diagnosis of AKI and prediction of death. We also assessed the relationship between total biomarker excretion and the severity of functional change in AKI.

METHODS: Urinary concentrations of Alkaline Phosphatase (AP), ɣ-Glutamyl Transpeptidase (GGT), Cystatin C, Neutrophil Gelatinase Associated Lipocalin (NGAL) and creatinine were measured on admission to the ICU, at 12h and 24h in patients in the EARLYARF trial. The average urine flow rate was calculated from 4-hour creatinine clearance measurements obtained at the same time points which allowed calculation of biomarker excretion rate. The performance of absolute and indexed biomarker concentration, and of excretion rate in diagnosis of AKI (AKIN definition: ≥0.3mg/dl or ≥50% increase in plasma creatinine from baseline) was assessed by receiver-operator characteristic curve (ROC) analysis, with comparison of the area under curve (AUC) performed using the DeLong method. Total excretion over 24h for each biomarker was calculated and the association with maximum AKIN stages within 48 hours was analyzed using one-way ANOVA.

RESULTS: A total of 484 patients were analyzed; 44 patients were excluded from analysis because of collection error and missing samples. For diagnosis, absolute biomarker concentration yielded the largest AUCs: AP: 0.54

(0.48 to 0.59); GGT: 0.66 (0.60 to 0.71); Cystatin C: 0.68 (0.62 to 0.73); and NGAL: 0.71 (0.66 to 0.76). All AUC values were marginally higher by 0.05 to 0.09 ($p<0.0001$) than for excretion rate or indexed biomarker concentrations. For prediction of 7-day mortality, indexed biomarkers demonstrated the greatest AUCs: AP: 0.62 (0.54 to 0.71); GGT: 0.65 (0.56 to 0.73); Cystatin C: 0.67 (0.59 to 0.74); and NGAL: 0.66 (0.58 to 0.74). These were larger by 0.04 to 0.09 compared to excretion rate and indexed biomarkers AUCs (indexed vs concentration: all biomarkers $p \leq 0.05$; indexed vs excretion rate: AP&GGT $p \leq 0.001$, Cystatin C&NGAL $p=0.06$). Total excretion of both Cystatin C and NGAL were correlated with maximum AKI severity ($p<0.0001$).

CONCLUSIONS: Indexing to creatinine or calculating a biomarker excretion rate did not improve the diagnostic utility of urinary biomarker concentration for AKI. However, for prediction of mortality, indexing to urine creatinine improved performance; this may result from capturing both cellular injury and loss of kidney concentrating function. Both NGAL and Cystatin C total excretion reflected the severity of renal dysfunction in AKI.

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