

Plasma biomarkers to identify patients at increased risk of chronic kidney disease (CKD) progression following an episode of acute kidney injury (AKI)

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Introduction

The long-term effects of acute kidney injury (AKI) on renal function and mortality are well documented. However, prospective studies are needed to develop strategies to identify patients at risk of developing subsequent chronic kidney disease (CKD) or progression of pre-existing CKD. We performed a study to test whether biomarkers predict CKD risk in people who have sustained AKI.

Methods

Participants who had sustained AKI during a hospital admission were recruited to a prospective cohort study. Participants had plasma samples collected at 3 months after hospitalisation and a panel of 14 biomarkers were measured using multiplex biochip array (Radox Teoranta, Donegal, Ireland). Renal function, proteinuria and survival were assessed at 1 and 3 years. CKD progression was defined as $\geq 25\%$ decline in eGFR from baseline (pre-AKI) with a decline in CKD stage.

Results

A total of 500 people who had sustained AKI and had samples available for biomarker assessment were studied. Median age was 70 years (IQR 13), AKI episodes were predominantly stage 1 with median duration 3 days (IQR 3) and 29% had pre-existing CKD. The number of participants who were still alive after three years without CKD progression was 266 (53%), 176 (35%) experienced CKD progression, and 46 (9%) died without pre-morbid CKD progression. Follow up data were unavailable for 12 (2%). Clinical factors associated with CKD progression included eGFR at 3months, albuminuria, AKI severity (stage) and duration of AKI.

A number of individual markers were associated with CKD progression at year 3. Multiplexed models were developed, and a model containing soluble tumour necrosis factor receptors (sTNFR) 1 and 2, cystatin C and creatinine had an AUC of 0.79 (95% CI 0.74-0.83) to discriminate participants who had CKD progression three years after AKI. Notably, the negative predictive value (NPV) of this model was 92% (95% CI 87-97%); corresponding sensitivity was 95%, specificity 39%, and positive predictive value 50%. Internal validation of this model with bootstrapping produced similar AUC values, suggesting minimal overfitting. Clinical data and biomarkers were then combined by constructing multiple decision trees that allowed selection and ranking of the variables that were most strongly associated with CKD progression at year 3. These analyses identified similar biomarkers (sTNFR 1 and 2 and cystatin C, plus NGAL) together three-month eGFR and urine albumin:creatinine ratio, all of which were more important than clinical variables describing AKI severity or duration (Figure 1).

Conclusions

A decline in renal function is common following AKI, even in a general hospital population with predominantly AKI stage 1. A biomarker model incorporating sTNFR1, sTNFR2 and cystatin C demonstrated utility in assessing AKI patients, 3 months after hospital discharge, for long-term CKD risk. Its high NPV

suggests potential clinical utility as a 'rule-out' test, to identify AKI patients who are at very low risk of subsequent CKD and who do not need additional follow up.