THE POTENTIAL OF URINARY BIOMARKERS TO IMPROVE RISK STRATIFICATION FOR CKD PROGRESSION: A PILOT STUDY

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Introduction and aims

Tubulo-interstitial damage is fundamental in progressive nephropathies and classical pathology studies showed that these alterations are more strongly related to the glomerular filtration rate (GFR) than glomerular changes. Whether established biomarkers of tubulo-interstitial damage like urine Neutrophil Gelatinase Associated Lipocalin (NGAL), Uromodulin and T-cell-immunoglobulin-Mucin (KIM-1) may serve to refine the prediction of the evolution of CKD toward kidney failure has not been tested in the CKD population.

Methods

We performed a pilot study in a cohort of 118 CKD patients (age 62±11; M 59%; 34.5±12.8 ml/min/1.73 m2) to test whether 24h urinary NGAL, Uromodulin and KIM-1 excretion may add meaningful prognostic power to eGFR to predict a composite renal outcome (eGFR decline >30%, dialysis or transplantation) over a 3-year follow-up. On the basis of the relationship (with P<0.10) between each urinary biomarker (re-codified in binary terms, i.e. below/above the corresponding median value) and the renal outcome, a composite risk score was developed by using multiple Cox regression analysis. The additional prognostic power of this score beyond and above that provided by eGFR was assessed by Cox regression and by C-statistics (Harrell's C Index).

Figures

Variable	HR	95% CI	P value
Urinary NGAL (24h)	4.0	1.7-9.6	0.002
Urinary Uromodulin (24h)	2.0	0.9-4.3	0.09
Urinary KIM 1 (24h)	2.5	1.0-5.8	0.04

Tab. 1. Multiple Cox regression model including NGAL, Uromodulin and KIM-1

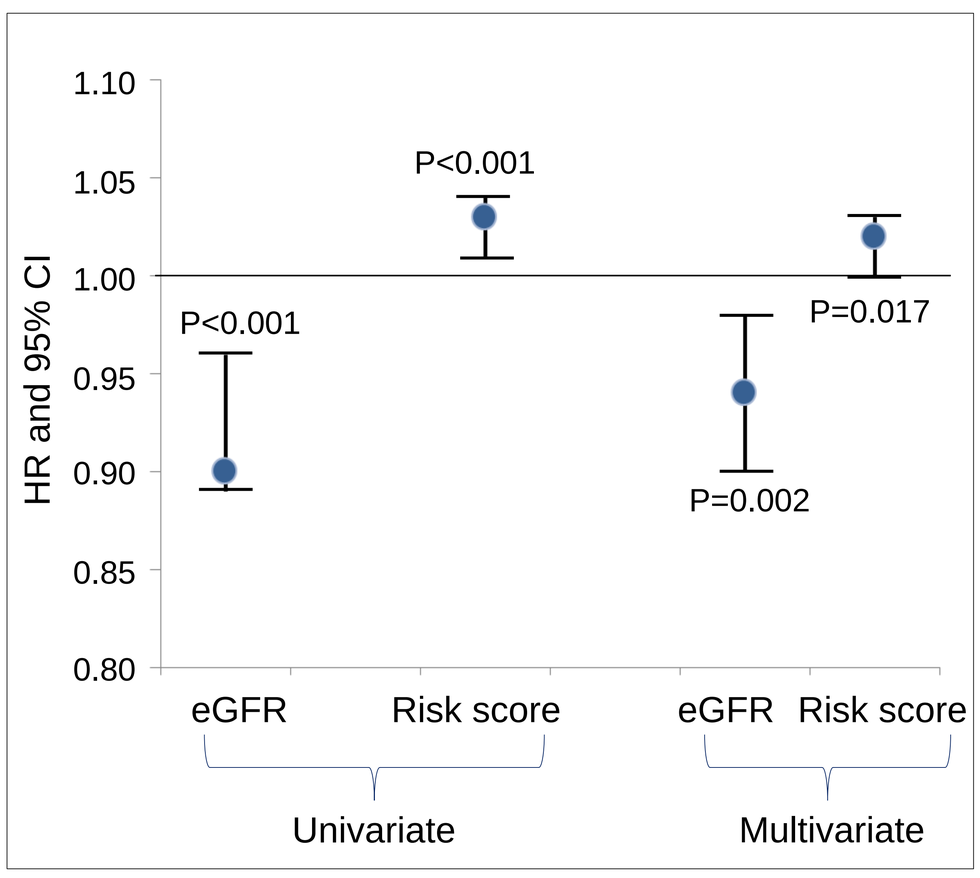

Fig. 1. Hazard ratio associated to eGFR and Risk score (Univariate and Multivariate Analyses) and 95% CI for the combined renal end-point

Results

During a 3-year follow-up, 31 patients had the renal outcome (10.4 events x 100 person-years). In a multiple Cox regression model, NGAL [HR:4.0, 95% CI: 1.7-9.6, P=0.002], Uromodulin [HR:2.0, 95% CI: 0.9-4.3, P=0.09] and KIM-1 [HR:2.5, 95% CI: 1.0-5.8, P=0.04] separately predicted the study outcome (Tab.1). Therefore, a score based on these biomarkers was derived. In two separate Cox regression models, both eGFR [HR (1 ml/min/1.73m2):0.9, 95% CI: 0.89-0.96] and the tubular-risk score [HR:1.03, 95% CI: 1.01-1.04] significantly associated to the combined renal end point (P<0.001). We then generated a combined model including both predictors. In this model both the eGFR, (HR:0.94, 95% CI: 0.90-0.98, P=0.002) and the risk score (HR: 1.02, 95% CI:1.0-1.03, P=0.017) retained an independent prediction power for the combined renal end-point suggesting that the tubular-risk score may provide prognostic information above and beyond that provided by the eGFR (Fig.1). Accordingly, the Harrell C index of a Cox model including eGFR + risk score (79%, P<0.001) was significantly higher (P=0.02) than that based on eGFR alone (77%, P<0.001).

Conclusions

A tubular risk score derived by urinary NGAL, Uromodulin and KIM-1 meaningfully improves the discrimination power of a model based on the eGFR. Findings in this pilot prognostic study suggest that markers of tubule-interstitial damage have potential for refining the risk stratification for renal function loss in CKD patients and form a basis for a large, full-fledged observational study to test the same hypothesis in an adequately powered scenario.

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