HIGH SOLUBLE UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR (sUPAR) IS A STRONG , INDEPENDENT PREDICTOR OF THE RISK OF WORSENING PROTEINURIA AND CKD PROGRESSION IN STAGE 2-5 CKD PATIENTS

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Introduction and aims

High plasma levels of soluble urokinase-type plasminogen activator receptor (sUPAR) predict incident CKD and accelerated decline in renal function in community levels studies in individuals with initially normal renal function. Whether high sUPAR associates with the risk of proteinuria worsening and progression to kidney failure in patients with established CKD is still unknown.

Methods

We measured plasma sUPAR (R&D ELISA) in 753 stage 2-5 CKD patients and measured the GFR (4-variable MDRD) and proteinuria over time and estimated the risk for GFR loss ($\geq$30%) or dialysis. Urine sUPAR and biomarkers of tubular injury (β_2 microglobulin, KIM-1 and NGAL) were measured in a subgroup of 118 patients. Data were analysed by the Linear Mixed Model (LMM) and Cox regression analysis adjusting for traditional risk factors and a large series of CKD-specific risk factors.

Figures

Variable	r	P
Age	r = 0.147	<0.001
Diabetes	r = 0.138	<0.001
Systolic BP	r = 0.177	<0.001
eGFR(mdrd 186)	r = -0.363	<0.001
Proteinuria	r = 0.145	<0.001
C Reactive Protein	r = 0.137	<0.001
Haemoglobin	r = -0.174	<0.001
ADMA	r = 0.224	<0.001
1,25 (OH)$_2$ Vit. D	r = -0.131	<0.001
25 OH Vit. D	r = -0.182	<0.001
FGF 23	r = 0.221	<0.001
Phosphorous	r = 0.199	<0.001
PTH	r = 0.245	<0.001
Urinary KIM 1 (24h)	r = 0.397	<0.001
Urinary NGAL (24h)	r = 0.445	<0.001
Urinary sUPAR (24h)	r = 0.489	<0.001
Urinary β_2 microglobulin	r = 0.510	<0.001

Tab. 1. Baseline correlates of sUPAR

Tab. 2. Unadjusted and fully adjusted LMMs showing proteinuria worsening overtime for each 500 pg/ml increase of suPAR

	Univariate analysis	Multivariate analysis
sUPAR (500 pg/ml)	0.09 (0.05 – 0.12) P<0.001	0.06 (0.01 – 0.11) P=0.02

Fig. 1. Main baseline correlates of sUPAR

Fig. 2. Hazard ratio associated to sUPAR levels and 95% CI for the combined end-point all cause mortality/renal events.
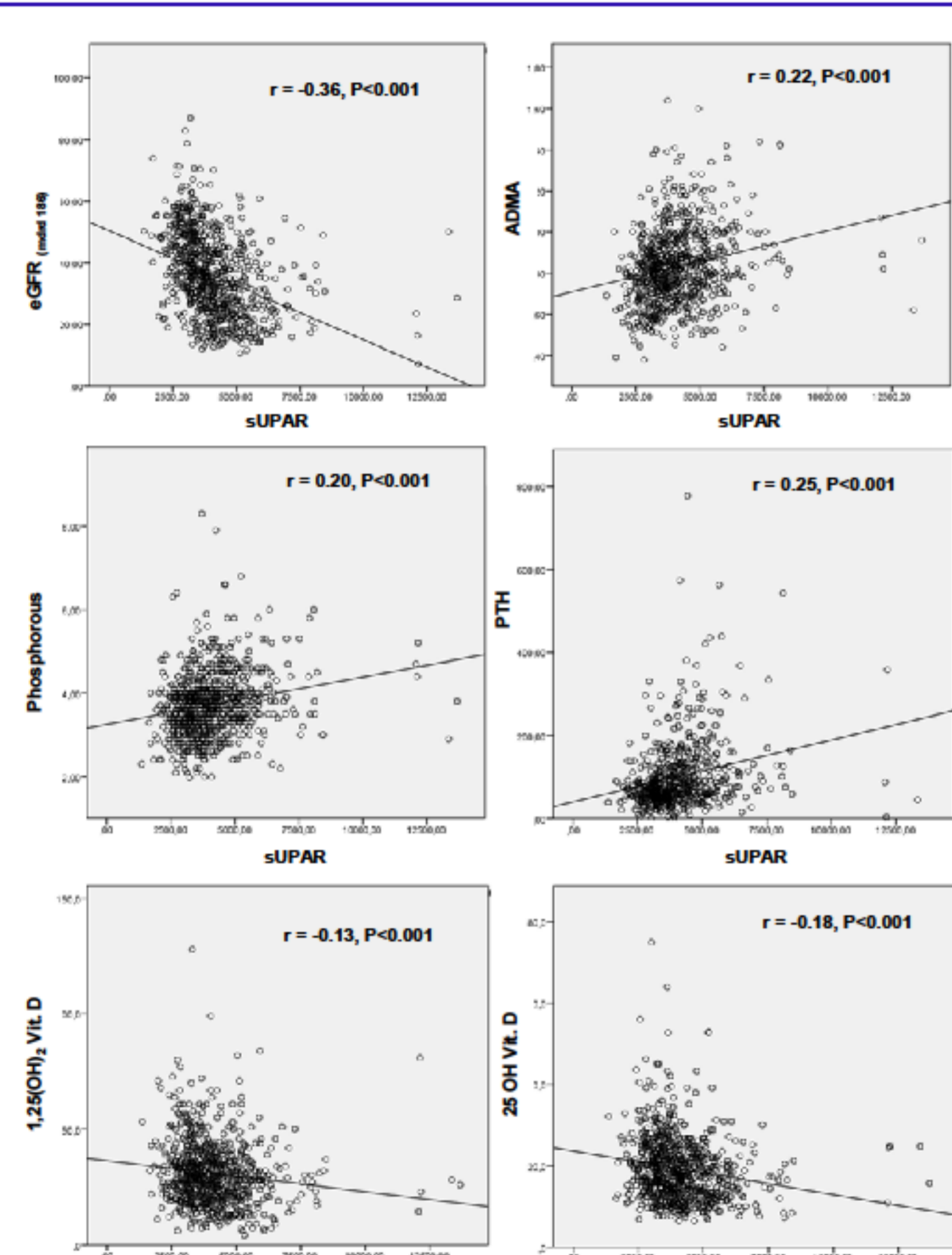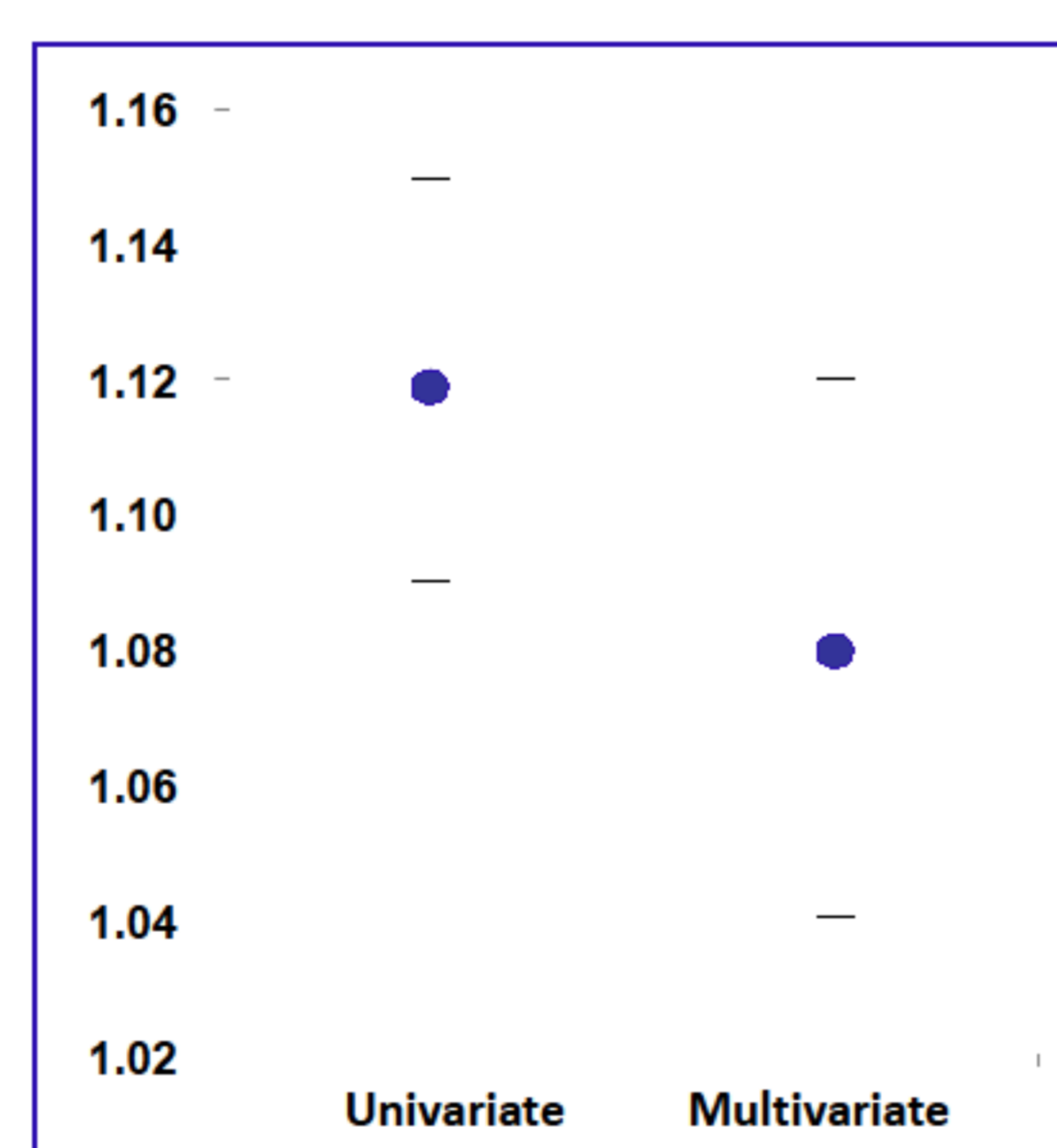
Results

At baseline sUPAR was higher in males and associated inversely with the GFR (r=-0.36, P<0.001) and directly with proteinuria (r=0.145, P<0.001). Furthermore sUPAR correlated positively with age, systolic BP, diabetes, C-Reactive Protein (CRP), phosphate, PTH, FGF23, ADMA and inversely with Hb, 25OH Vit.D and 1,25(OH)$_2$ Vit.D (all P<0.001). In the subgroup with available urine biomarkers circulating sUPAR correlated strongly with 24h urine sUPAR (r=0.49) as well as β_2 microglobulin (r=0.51), KIM-1 (0.44) and NGAL (0.40) (all P<0.001). Over a 31$\pm$10 months follow-up sUPAR predicted proteinuria worsening overtime in unadjusted and fully adjusted LMMs. Forty-two patients died and 243 had a renal event. sUPAR was a strong predictor of the combined end-point death and GFR loss $\geq$30% or dialysis [HR (500pg/ml): 1.12, 95%CI: 1.09-1.15] in a Cox's regression analysis adjusting for a large series of potential confounders including background cardiovascular disease, the GFR, proteinuria, age, gender, smoking, diabetes, systolic BP and anti-hypertensive treatment, phosphate, Hb, serum albumin, BMI, CRP, ADMA and FGF23.

Conclusions

Elevated sUPAR levels associate with lower GFR, proteinuria and tubular injury and a large series of CKD-specific risk factors including Hb, biomarkers of CKD-MBD, FGF23 and ADMA. sUPAR is a robust predictor of worsening proteinuria over time and in fully adjusted Cox's regression analyses sUPAR maintains a strong predictive power for a combined end point including death and GFR loss $\geq$30% or dialysis. These findings support the contention that sUPAR is causally implicated in the progression toward kidney failure in CKD patients.