Collagen Turnover and Fibrogenesis Biomarkers Associate with Kidney Disease Progression in CKD: Data from CRIC and NURTuRE-CKD

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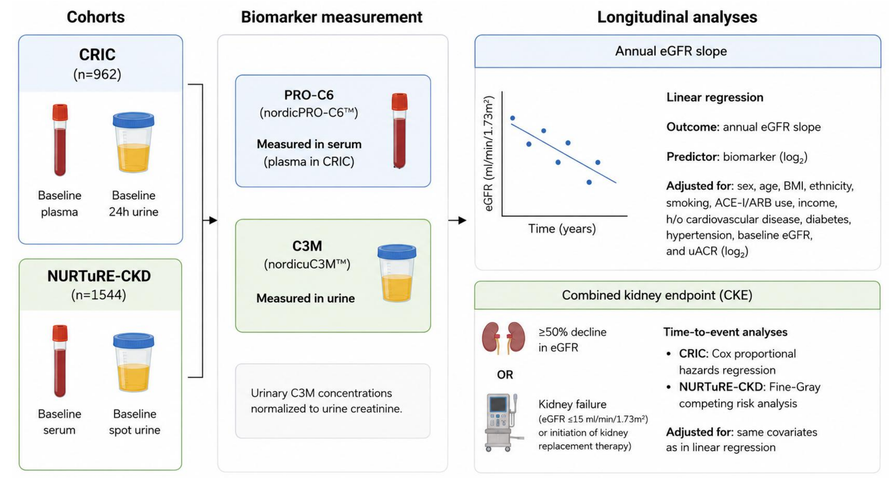
BACKGROUND

Fibrosis is a central pathogenic process in CKD progression, and biomarkers reflecting this process may offer prognostic value. Circulating PRO-C6, a pro-fibrotic signaling and tissue formation fragment of type VI collagen, and urinary C3M, an immune cell-mediated degradation fragment of type III collagen, have been previously explored in CKD cohorts, showing prognostic value in patients with different etiologies.

The aim of this study was to validate the prognostic potential of PRO-C6 and uC3M in two large well-characterized, prospective, multicenter non-dialysis CKD cohorts.

METHODS



RESULTS

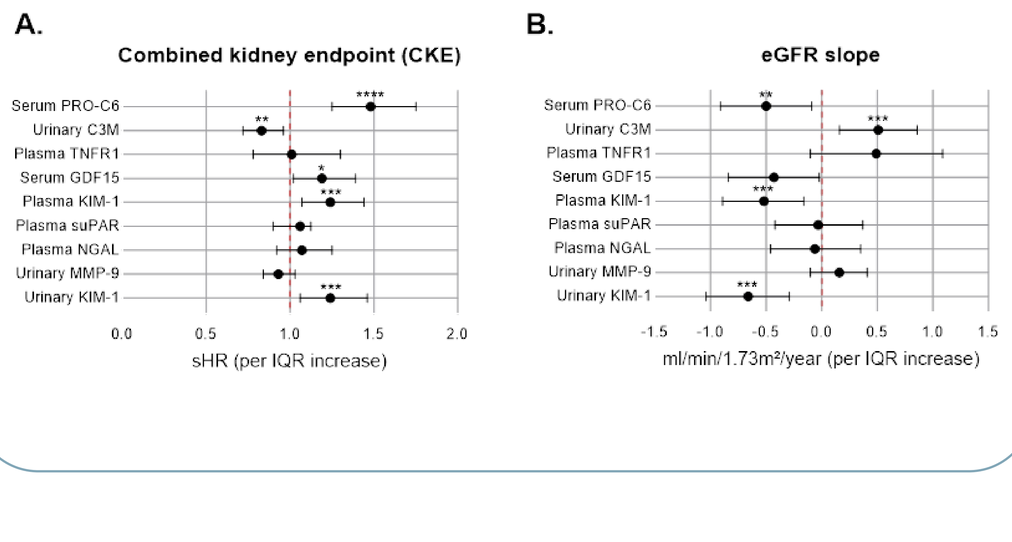
SUMMARY OF RESULTS

- In the follow-up periods of 6.9 years in CRIC and 3.9 years in NURTuRE-CKD, the combined kidney endpoint (CKE: ≥50% decline in eGFR or kidney failure) occurred in 42.1% and 39.5% of participants.
- **High levels of circulating PRO-C6** and **low levels of urinary C3M** were independently associated with the **occurrence of a CKE and annual eGFR slope**;
- Higher levels of **circulating PRO-C6** were also associated with an increased **risk of death**;
- Circulating PRO-C6 and urinary C3M **association with CKE** was **stronger than** markers of kidney injury and inflammation (**NGAL, TNFR1, GDF15, suPAR, MMP-9**) and had a similar but independent prognostic value than KIM-1.

ALL-CAUSE MORTALITY

		CRIC		NURTuRE-CKD	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
PRO-C6 (Measured in serum (plasma in CRIC))	Log_2	1.81 (1.48-2.22)	**<0.001**	2.25 (1.77-2.86)	**<0.0001**
	Tertiles				
	1	Reference		Reference	
	2	1.51 (1.10-2.13)	**0.02**	1.06 (0.67-1.63)	0.80
	3	2.38 (1.63-3.46)	**<0.001**	1.89 (1.21-2.95)	**0.005**

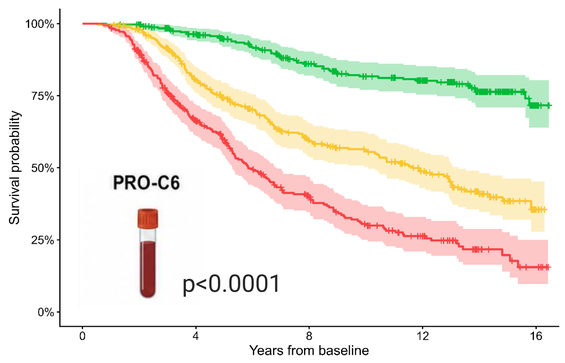
BENCHMARKING WITH OTHER KIDNEY MARKERS



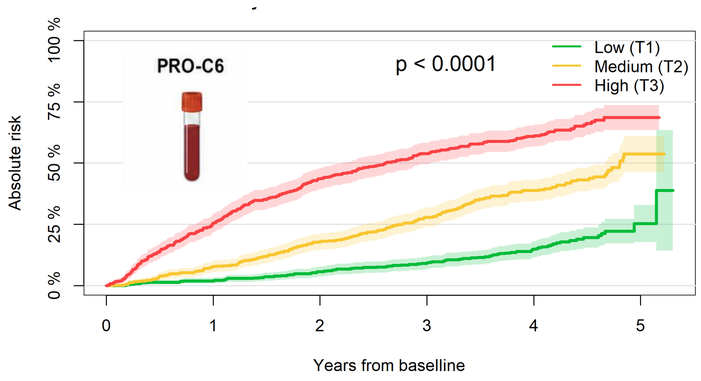
KIDNEY DISEASE PROGRESSION

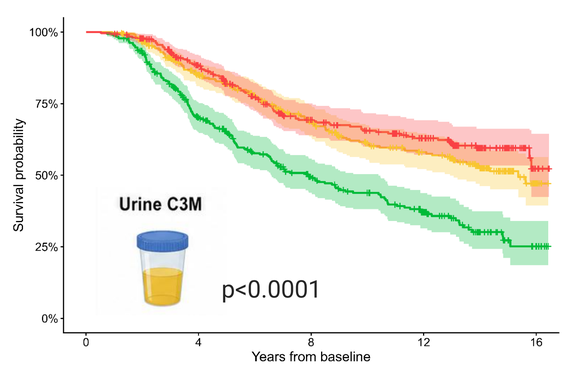
		CRIC				NURTuRE-CKD			
		Combined kidney endpoint		eGFR slope		Combined kidney endpoint		eGFR slope	
		Hazard ratio (95% CI)	*p*-value	β-coefficient (95% CI)	*p*-value	sHazard ratio (95% CI)	*p*-value	β-coefficient (95% CI)	*p*-value
PRO-C6 (Measured in serum (plasma in CRIC))	Log_2	1.82 (1.48-2.23)	**<0.001**	-0.81 (-1.14 to -0.48)	**<0.001**	1.80 (1.52-2.14)	**<0.0001**	-0.78 (-1.22 to -0.34)	**0.0006**
	Tertiles								
	1	Reference		Reference		Reference		Reference	
	2	1.42 (1.01-1.98)	**0.04**	-0.49 (-0.93 to -0.05)	**0.03**	1.34 (1.03-1.74)	**0.03**	-0.05 (-0.17 to 0.86)	0.86
	3	1.82 (1.25-2.65)	**0.002**	-1.08 (-1.60 to -0.56)	**<0.001**	2.11 (1.59-2.80)	**<0.0001**	-0.42 (-1.27 to 0.21)	0.21
Urine C3M (Measured in urine (normalized to creatinine))	Log_2	0.87 (0.79-0.96)	**0.006**	0.27 (0.10-0.45)	**0.002**	0.85 (0.74-0.97)	**0.017**	0.51 (0.14 to 0.87)	**0.006**
	Tertiles								
	1	Reference		Reference		Reference		Reference	
	2	0.74 (0.58-0.94)	**0.01**	0.42 (0.01-0.83)	**0.04**	0.72 (0.60-0.86)	**0.0003**	0.42 (-0.09 - 0.94)	0.11
	3	0.71 (0.55-0.93)	**0.01**	0.59 (0.16-1.02)	**0.007**	0.77 (0.63-0.95)	**0.01**	0.80 (0.26 - 1.34)	**0.004**

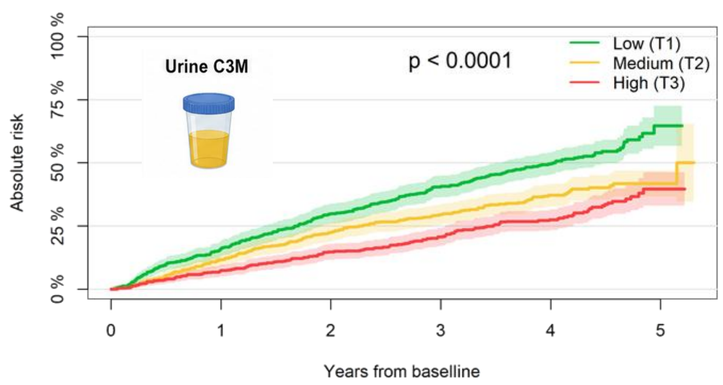
CRIC



NURTuRE-CKD







NORDIC BIOSCIENCE

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Disclosures: SSG and FG are employed at Nordic Bioscience and may be shareholders.

CONCLUSION

Increased circulating PRO-C6 and decreased urinary C3M are independently associated with kidney disease progression and a more rapid decline in eGFR. Increased circulating PRO-C6 is also associated with risk of death.

PRO-C6 and C3M provide mechanistic insights into collagen remodeling and fibrogenesis processes during CKD progression that are not captured by conventional markers of kidney function such as eGFR and UACR and kidney injury markers.