URINE NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (uNGAL) MEASURED IN CHRONIC KIDNEY DISEASE STAGE-3 AS A PREDICTOR OF PROGRESSION OF CHRONIC KIDNEY DISEASE.

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Introduction

- Chronic kidney disease (CKD) is a global public health concern with a steady increase in the prevalence of patients reaching end-stage and requiring renal replacement therapy (RRT) (1, 2).
- CKD is associated with an increased risk of cardiovascular events and all-cause mortality (3).
- There is a wide variation in degree and rate of progression of CKD of diverse etiology and stage of CKD.

- In recent years, much research has focused on identifying groups that are at a high risk of rapid progression in CKD and tools to distinguish these patients from those with impaired but stable kidney function.
- Several clinical predictors of CKD progression such as poor control of hypertension and heavy proteinuria or albuminuria are used in clinical practice (4,5), but the biomarker-guided prediction of CKD progression is another promising tool that is not sufficiently explored.
- We measured urine neutrophil gelatinase-associated lipocalin (uNGAL), a renal tubular injury marker, in patients with CKD stage III and followed them to determine its accuracy in predicting the progression of CKD.

Aim of the study

- To evaluate the role uNGAL in predicting the progression of CKD stage III patients.

Subjects and methods

- We measured uNGAL in 91 patients with CKD stage 3.
- Demographic data such as age, sex, serum creatinine, blood urea, urine protein creatinine ratio, were collected at the time of measurement of uNGAL and

  level > 150 ng/ml was considered elevated.
- Estimated glomerular filtration rate(eGFR) was calculated at baseline and at last follow up according to 4 variable modification of diet in renal disease (MDRD) equation.

Selection criteria

Inclusion criteria

- Adult patients of both genders, with CKD stage 3 (eGFR: 30-60 ml/min/1.73 m^2).
- Patients who are on regular follow up in our unit for at least last 6 months.
- Patients with stable renal function, without any AKI episode preceding 3 months.
- Patients who are willing to give consent for participation in the study.

Exclusion criteria

- Patients aged <18 years.
- Patients with GFR ≤ 30 ml/min (National Kidney Foundation stage IV and V) or > 60 ml/min; malignancy; liver, thyroid, or infectious diseases (HBV, HCV, HIV, Tuberculosis); inflammatory states; post-transplant patients and treatment with steroids or immunosuppressive medications

Outcomes

- The primary composite end-point of our study was decline in the GFR >50% or RRT initiation.
- The secondary outcome was rate of decline of eGFR.

Results

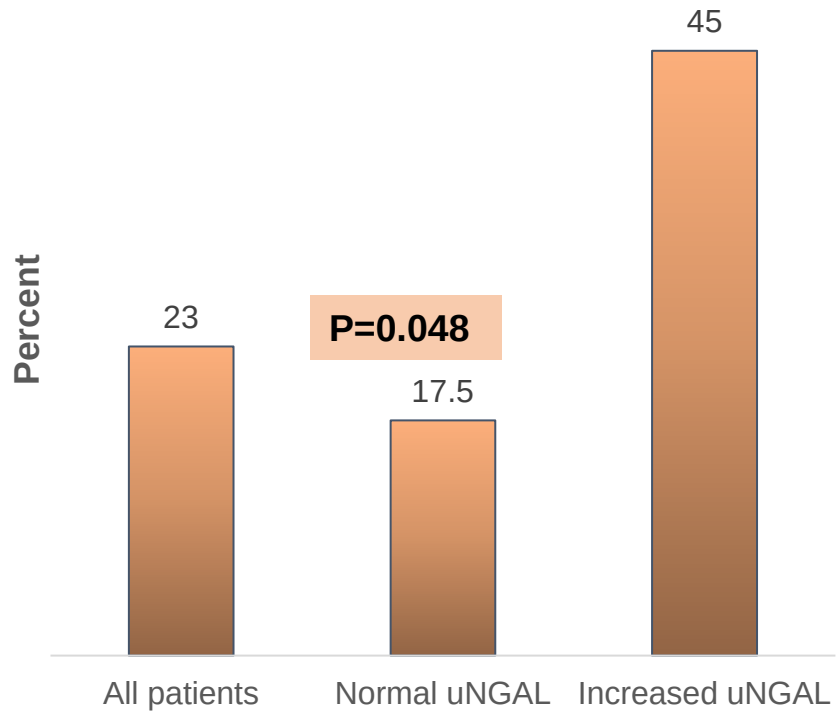
- The mean age was 52.13 ± 11.89 years, and 68 % were males.
- The mean duration of follow up was 34.3 ± 17.6 months.
- The mean uNGAL was 76.5 ± 130 ng/ml and 11 patients (12%) had elevated uNGAL of >150 ng/ml.
- Nineteen patients (20.8%) reached primary end point and mean decline in eGFR was -2.27 ± 10.4 ml/min/yr.

Table 1: Baseline characteristics of study population

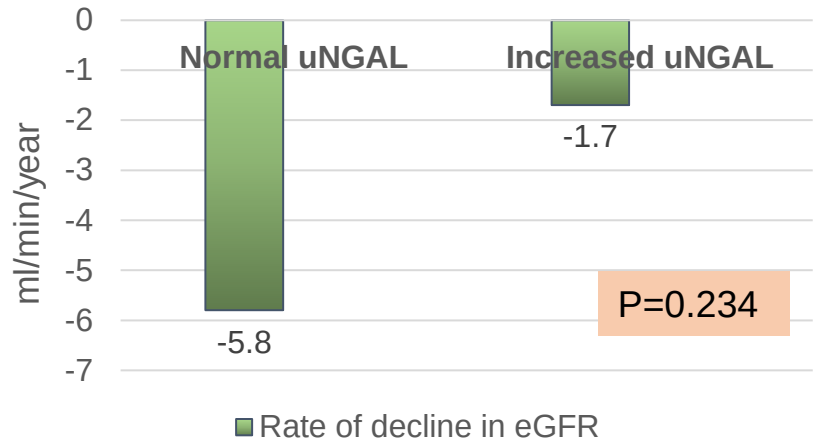
Baseline characteristics	Total (n=91)	Normal uNGAL(<150 ng/ml) (n=80)	Increased uNGAL(>150 ng/ml) (n=11)	P value
Age(Years)	52.1 ±11.9	52.96 ±11.42	46.09 ±14.05	0.72
Sex, male (%)	62 (68%)	56 (70%)	6 (55%)	0.32
SBP (mm Hg)	137.5 ±11.0	137.10 ±17.65	140.54 ±11.52	0.53
DBP (mm Hg)	82.4 ±8.6	81.96 ±8.53	85.27 ±8.63	0.23
Blood urea(mg/dl)	40.8 ±13.8	41.43 ±14.17	35.81 ± 9.50	0.20
Serum creatinine(mg/dl)	1.77 ±0.32	1.75 ±0.31	1.89 ±0.35	0.17
eGFR(mL/min/1.73 m^2)	42.3 ±8.2	42.57 ±8.16	40.42 ±8.61	0.41
Serum albumin(gm/dl)	4.01 ±0.51	4.04 ±0.44	3.78 ±0.80	0.10
UPCR(gm/gm)	1.92 ±3.6	1.46 ±3.34	5.17 ±3.93	0.01
VBG HCO3	23.45 ±2.96	23.64 ±2.90	22.01 ±3.1	0.87
uNGAL	76.54 ±129.9	37.43 ±34.60	360.90 ±203.09	<0.01
ACE/ARB (%)	60 (65.9%)	53 (66.2%)	7(64%)	0.86

Outcomes of the study

Primary outcome



Rate of decline in eGFR



The sensitivity and specificity of uNGAL cut-off value of 150 ng/ml to predict primary outcomes were **45.5%** and **82.5%** respectively.

uNGAL for prediction of primary endpoint.

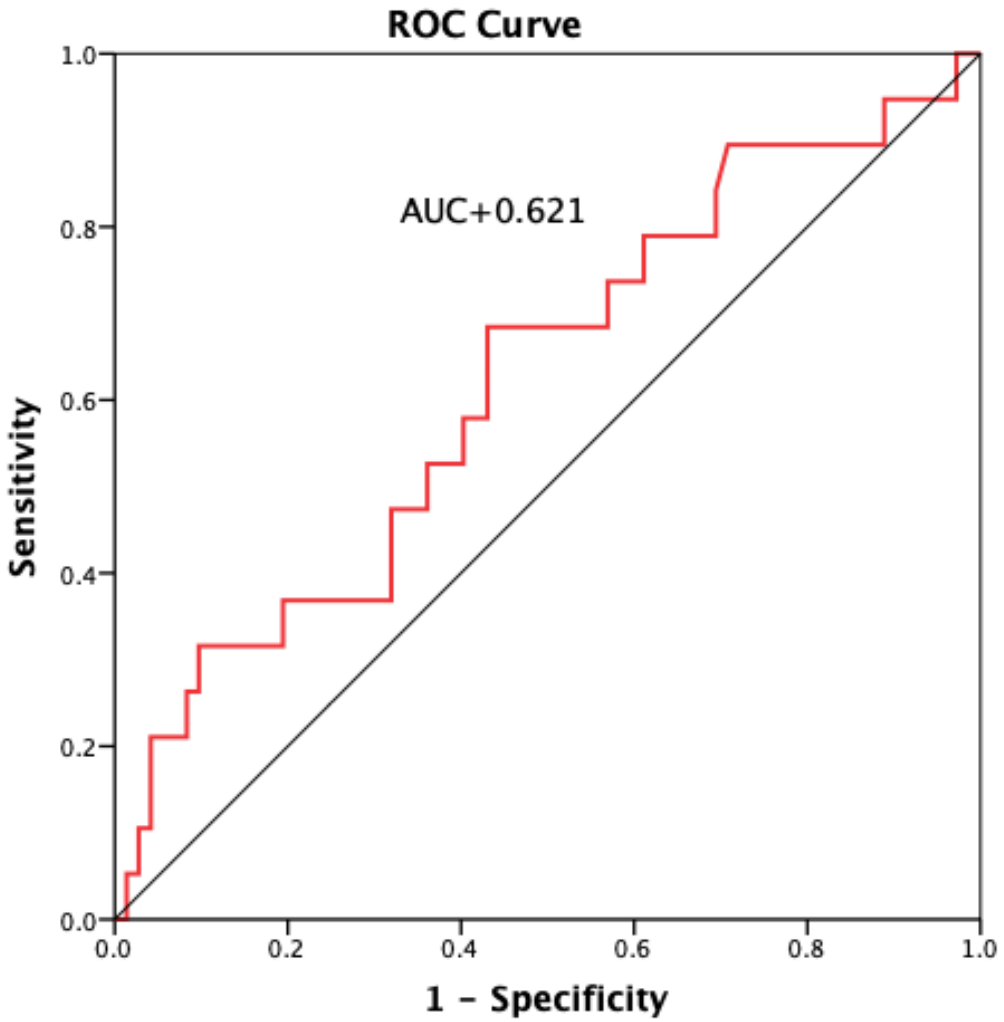


Table 2: Logistic regression of predictors of primary outcome

Variable	B	SE	Exp(B)	95% CI of Exp(B)	P Value
Age	-0.025	0.024	0.976	0.932-1.022	0.3
Sex	-0.29	0.736	0.748	0.177-3.16	0.694
Systolic BP	0.004	0.022	1.004	0.962-1.048	0.851
Diastolic BP	0.001	0.046	1.001	0.914-1.096	0.98
Baseline eGFR	-0.067	0.042	0.935	0.862-1.015	0.11
Urine PCR	0.051	0.73	1.053	0.912-1.215	0.48
uNGAL	0.001	0.002	1.001	0.997-1.005	0.57
Serum albumin	-0.560	0.47	0.571	0.228-1.4330.223	
VBG-HCO3	-0.035	0.112	0.966	0.774-1.204	0.76
Constant	5.072	4.38	159.5		0.25

Table 3: Comparison of studies

Study	N	Study populations	End-point, (Dur FU)	Results	Remarks
Smith et al (NDT 2013	158	CKD stage 3 and 4	ESRD or death (2 years)	Urine NGAL/Cr ratio: HR per 5 µg/mmol increase 1.27, 95% CI: 1.01-1.60, P = 0.036	uNGAL/uCr ration was an independent predictor of endo-point
Bolignano et al (CJASN 2009)	96	CKD stage 3 to 4	Doubling of SCr or ESRD (18.5 months)	AUC of ROC: 0.78	uNGAL was a strong and indepedent predictor of progression of CKD
Liu et al (KI 2013)	3386	CRIC cohort, median eGFR 42 ml/min	>50% decline in eGFR or ESRD (3.2 years)	uNGAL HR: 1.7	Independent predictor of progression, but did not improve prediction model of progression of CKD
Patel et al (Ind J nephrol 2016)	91	CKD 2 to 4	Decline in eGFR <15 ml/min (18 months)	AUC of ROC: 0.778	Strong predictor of progression of CKD
Our study	91	CKD stage 3	>50% decline in eGFR or ESRD (34.5 months)	AUC of ROC: 0.621	Modest predictor of progression of CKD in stage 3

Strengths and Limitations of our study

Strengths

- Ours is one of the very few studies done on tubular injury marker- uNGAL as a predictor of progression of CKD.
- This is only one study from India in which we studied a considerable number of the population of CKD stage III.
- Duration of follow up of 34 months is longer than most similar studies.

Limitations

- Ours was a single-center study, and the cohort of patients was relatively small.
- Urine NGAL concentration was ascertained only at one point in time. Serial assessment may be more sensitive to predict progression.

Conclusions

- uNGAL was elevated in 12% of patients with CKD stage 3.
- uNGAL was significantly higher in patients who reached primary outcome of decline in eGFR >50% or ESRD over a mean duration of follow up of 34 months
- The predictive ability of uNGAL for rapid progression of CKD was modest (AUC=0.621)
- Our result suggests that uNGAL does not accurately predict the progression of stage 3 CKD in the Indian population.

References

(1) Lan PG, Johnson DW, McDonald SP, Boudville N, Borlace M, Badve SV, Sud K, Clayton PA. The association between peritoneal dialysis modality and peritonitis. Clinical Journal of the American Society of Nephrology. 2014 Mar 13:CJN-09730913.

(2) Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. Jama. 2011 Jun 15;305(23):2432-9.

(3)Go AS, Chertow GM, Fan D. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. Journal of Vascular Surgery. 2005 Jan 31;41(1):177.

(4) Kent DM, Jafar TH, Hayward RA, Tighiouart H, Landa M, de Jong P, de Zeeuw D, Remuzzi G, Kamper AL, Levey AS, AIRPD Study Group. Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. Journal of the American Society of Nephrology. 2007 Jun 1;18(6):1959-65.

(5)Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, Rogers NL, Teschan PE, Beck G, Modification of Diet in Renal Disease Study Group. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. Kidney international. 1997 Jun 1;51(6):1908-19.