

DAPAGLIFLOZIN AMELIORATES ISCHEMIA REPERFUSION RENAL INJURY VIA HIF1 INDUCTION.

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INTRODUCTION:

Growth differentiation factor 15 (GDF 15) is a member of the transforming growth factor- β superfamily. It is reported that GDF15 could be a useful prognostic marker in patients with chronic inflammatory disease and heart disease. We evaluated the role of serum GDF15 as an independent marker of renal outcome in immunoglobulin A nephropathy(IgAN).

METHODS:

212 patients in a Chungnam National Hospital glomerulonephritis cohort, who were diagnosed with biopsy-proven IgA nephropathy from March 2010 to June 2014, were included. GDF 15 was analyzed using an enzyme-linked immunosorbent assay. Correlations among initial serum GDF 15, blood urea nitrogen levels, serum creatinine level and estimated glomerular filtration rate (eGFR) and histologic renal inflammation and fibrosis were evaluated.

RESULTS :

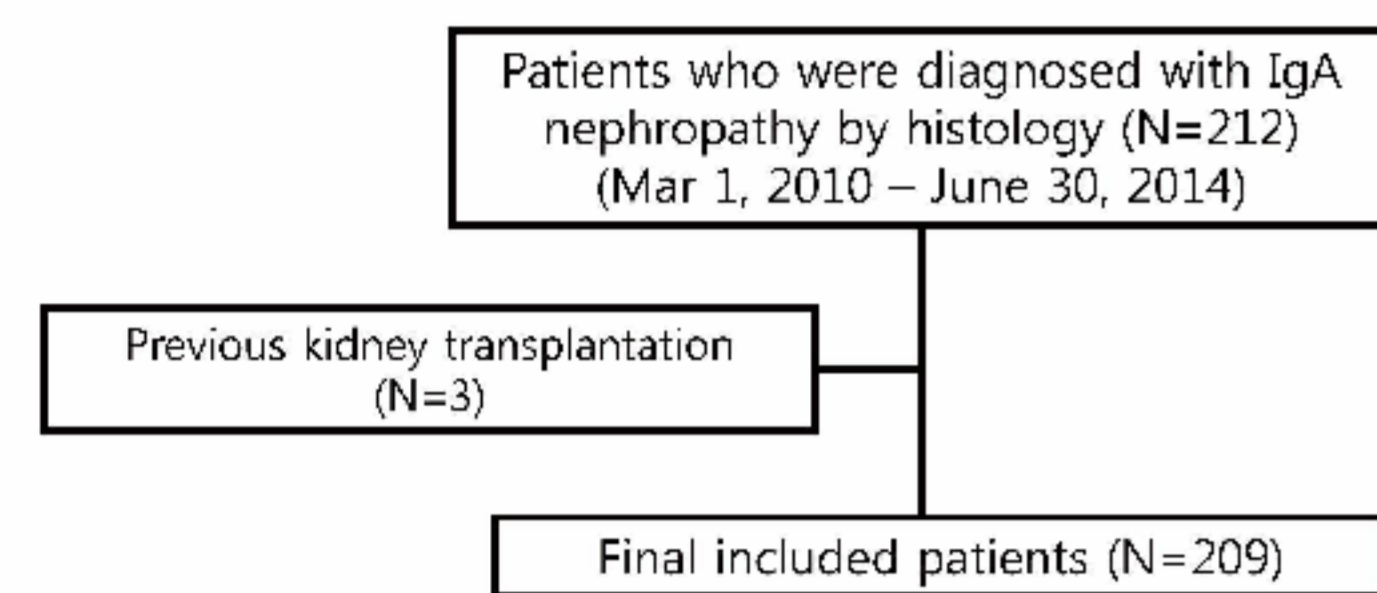


Figure 1. Study design

Pearson's coefficient	UPC	UPCR*	p*	GDF15	GDF15*	p*
Age	0.247**			0.468**		
BMI	0.069			-0.023		
Albumin	-0.587**	-0.549	0.000	-0.472**	-0.384	0.000
BUN	0.219	0.158	0.023	0.646**	0.605	0.000
Cr	0.166	0.141	0.042	0.623**	0.651	0.000
eGFR	-0.257**	-0.159	0.022	-0.649**	-0.549	0.000
BUN at 1y	0.109	0.170	0.075	0.278**	0.392	0.000
Cr at 1y	0.155	0.109	0.256	0.353**	0.410	0.000
eGFR at 1y	-0.186**	-0.146	0.128	-0.510**	-0.371	0.000
Δ eGFR at 1y	0.141	-0.106	0.269	-0.207*	-0.309	0.001
BUN at 2y	0.174	0.142	0.120	0.418**	0.377	0.000
Cr at 2y	0.163	0.155	0.090	0.371**	0.418	0.000
eGFR at 2y	-0.079**	-0.052	0.568	-0.431**	-0.323	0.000
Δ eGFR at 2y	0.267**	-0.245	0.007	-0.335**	-0.388	0.000

Table 2. Analysis of correlation BMI; Body mass index, BUN; Blood urea nitrogen, Cr; Serum creatinine, eGFR; Estimated glomerular filtration rate, y; Year

N=209	
Age (Mean \pm SD)	39.51 \pm 14.79
Male (n, %)	103, 49.3%
BMI (Mean \pm SD)	23.814 \pm 4.66
Past medical history (n, %)	
HTN	32, 15.3%
DM	19, 9.1%
HBV carrier	4, 1.9%
Solid cancer	10, 4.8%
Initial laboratory data	
BUN (mg/dL)	17.84 \pm 10.02
Creatinine (mg/dL)	1.24 \pm 1.25
eGFR (MDRD)	86.09 \pm 36.46
UPCR (mg/g)	1.7 \pm 2.58
GDF15 (pg/mL)	426.34 \pm 398.57

Table 1. Baseline characteristics

BMI: Body mass index; HTN: Hypertension; DM: Diabetes mellitus; HBV: Hepatitis B virus; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; UPCR: Urine protein creatinine ratio; GDF: Growth differentiation factor
Note: Conversion factors for units: SCr in mg/dL to μ mol/L, x88.4; BUN in mg/dL to mmol/L, x0.357;

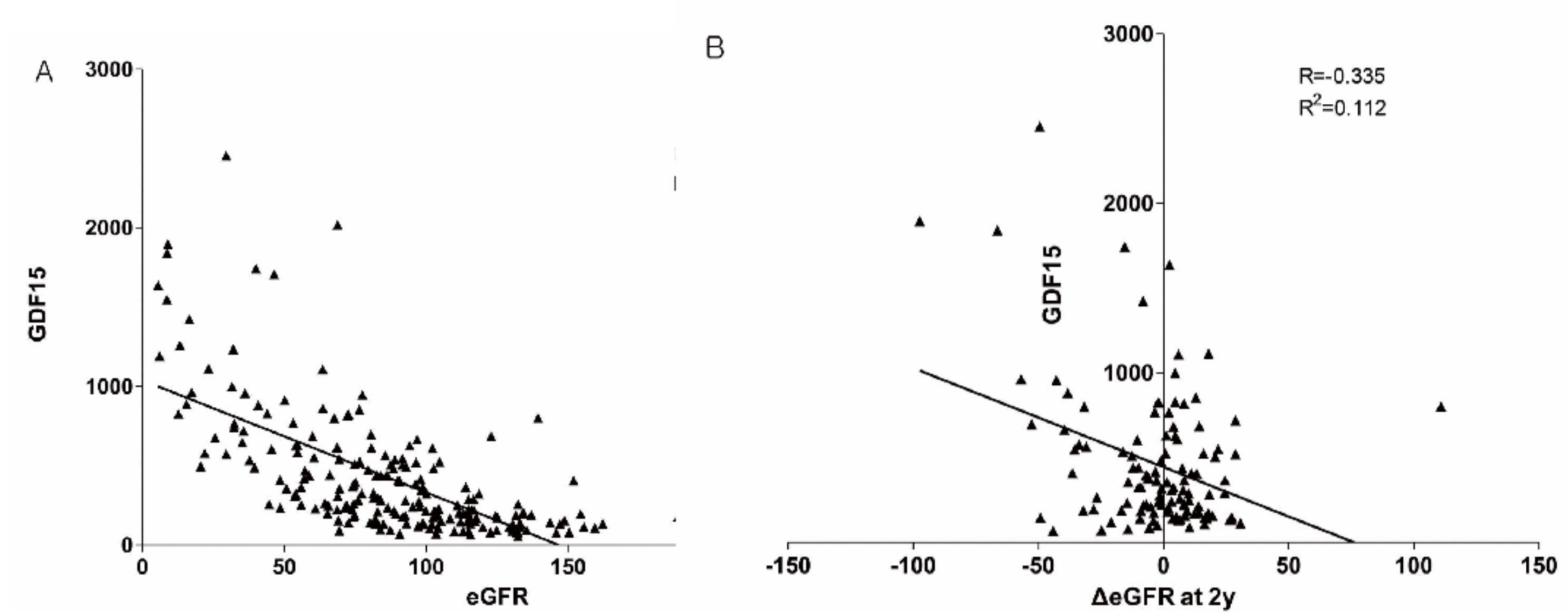


Figure 2. The analysis of correlation between eGFR and GDF 15 Initial serum growth differentiation factor 15 (GDF 15) level was correlated with initial estimated glomerular filtration rate (eGFR) and the 2 year follow-up eGFR. A: The scatterplot between GDF 15 and initial eGFR was correlated (r, -0.649). B: Initial serum GDF 15 level was correlated with 2 year Δ eGFR (r, 0.335).

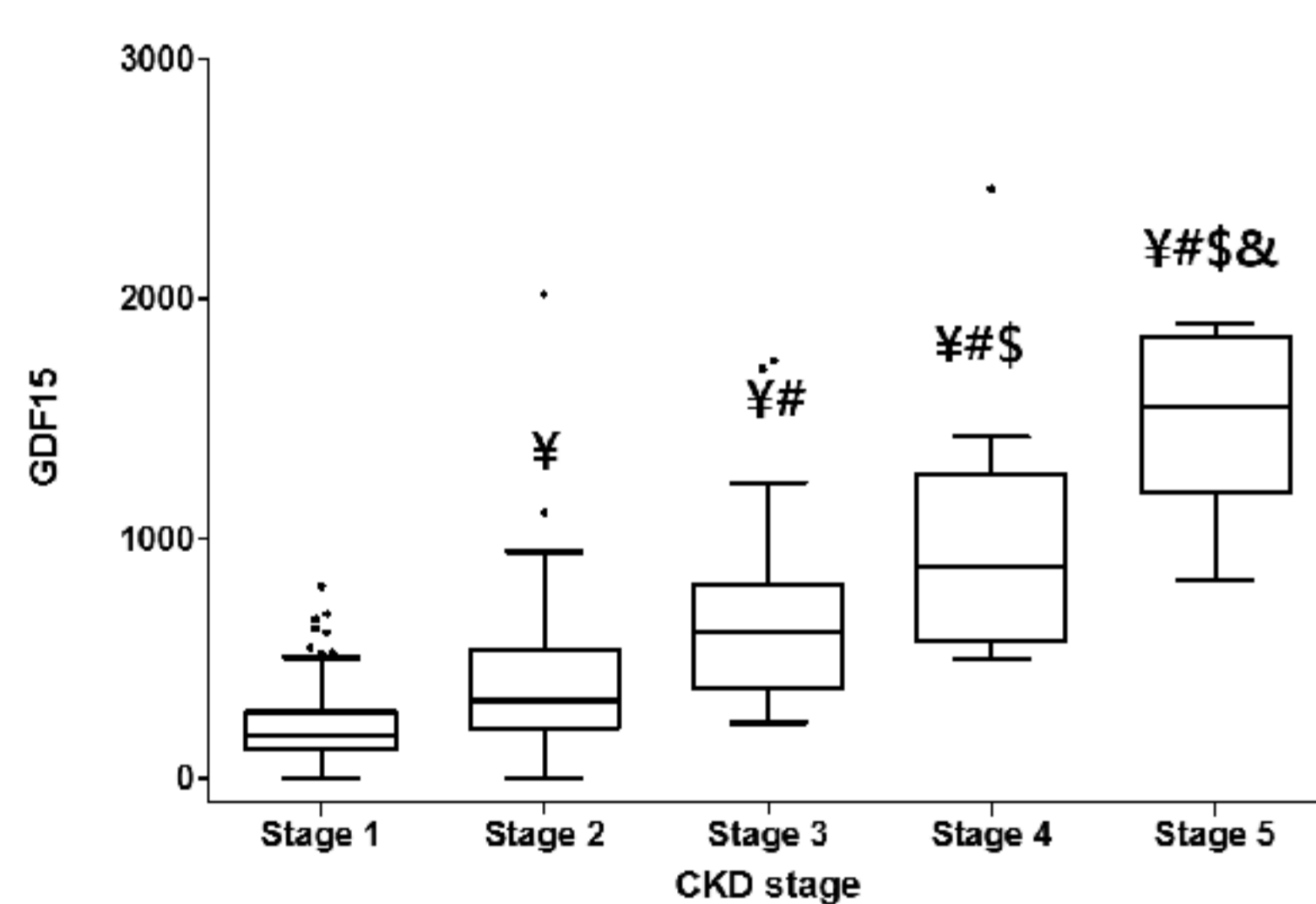


Figure 3. The correlation between CKD stages and GDF 15 Differences in initial serum GDF 15 level among chronic kidney disease (CKD) stages. The means of each group were significantly different according to Tukey's multiple comparison test. Initial serum GDF 15 level was higher in patients with a higher CKD stage than those with a lower CKD stage.

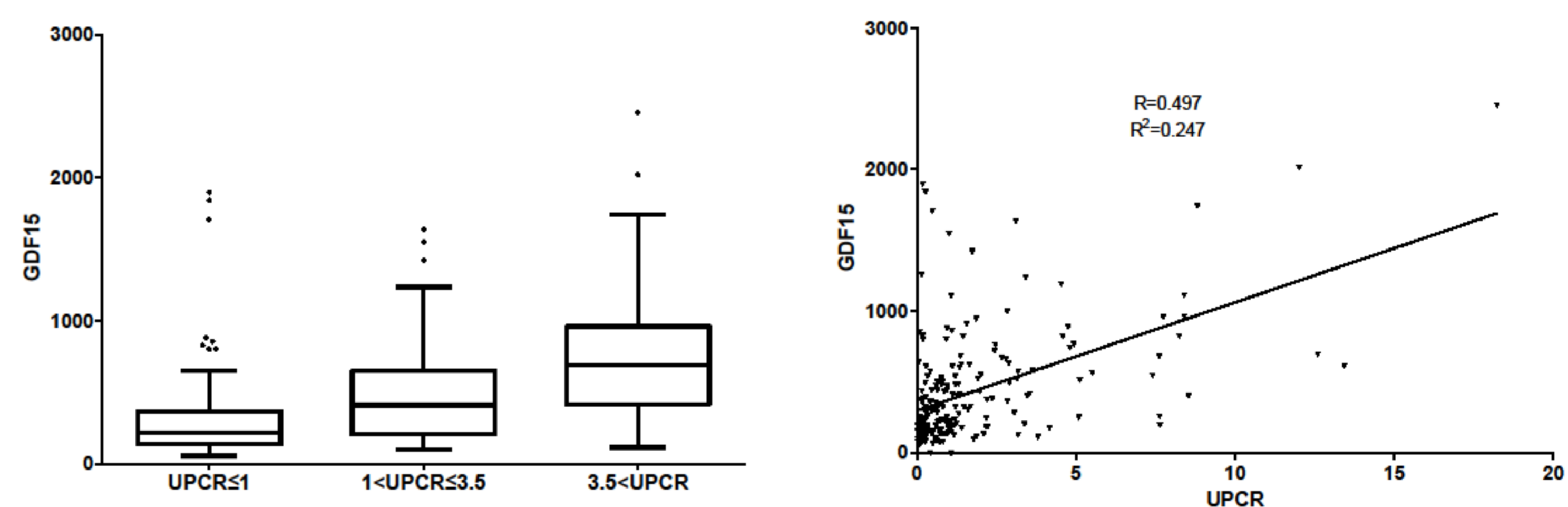


Figure 4. The correlation between proteinuria and GDF 15 Initial serum GDF 15 was correlated with the initial urine protein creatinine ratio (UPCR). A: Initial serum GDF 15 was correlated with initial UPCR (r, 0.497). B: The UPCR was divided into three groups. A UPCR of 1 g/g was the cutoff value to start medication in patients with IgA nephropathy and a UPCR of 3.5 g/g was defined as nephrotic syndrome. Higher proteinuria indicated a higher initial serum GDF 15 level.

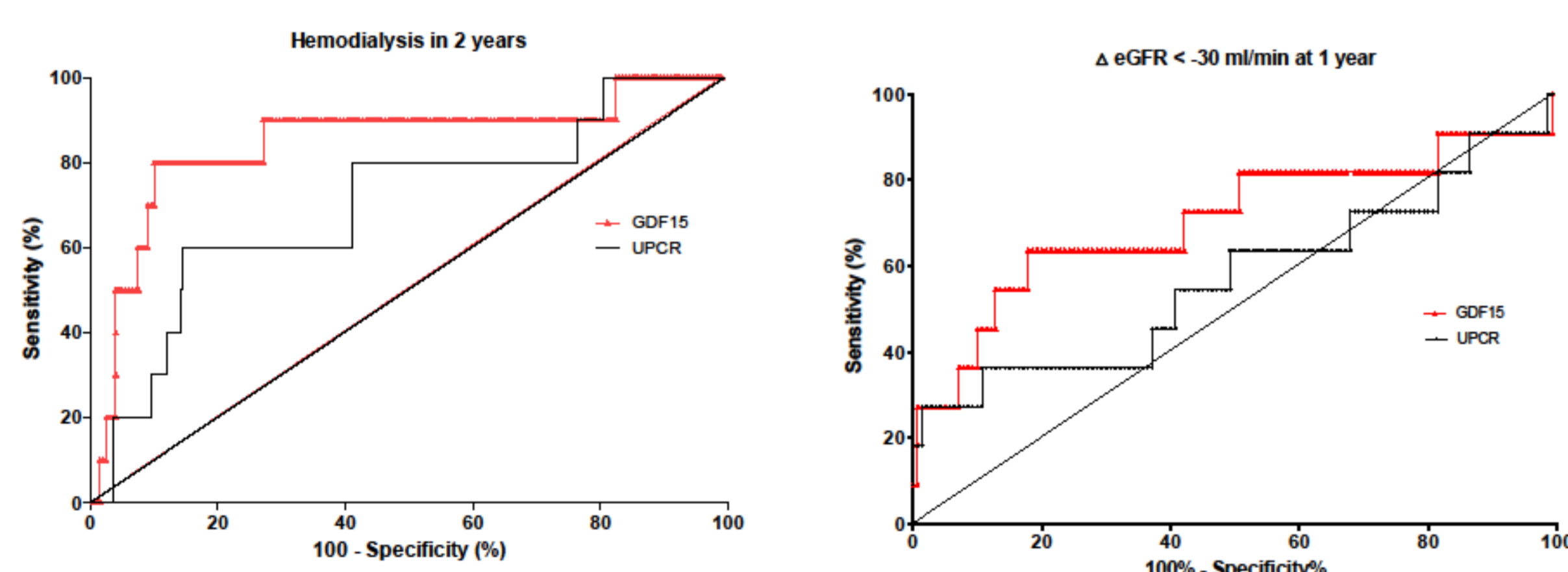
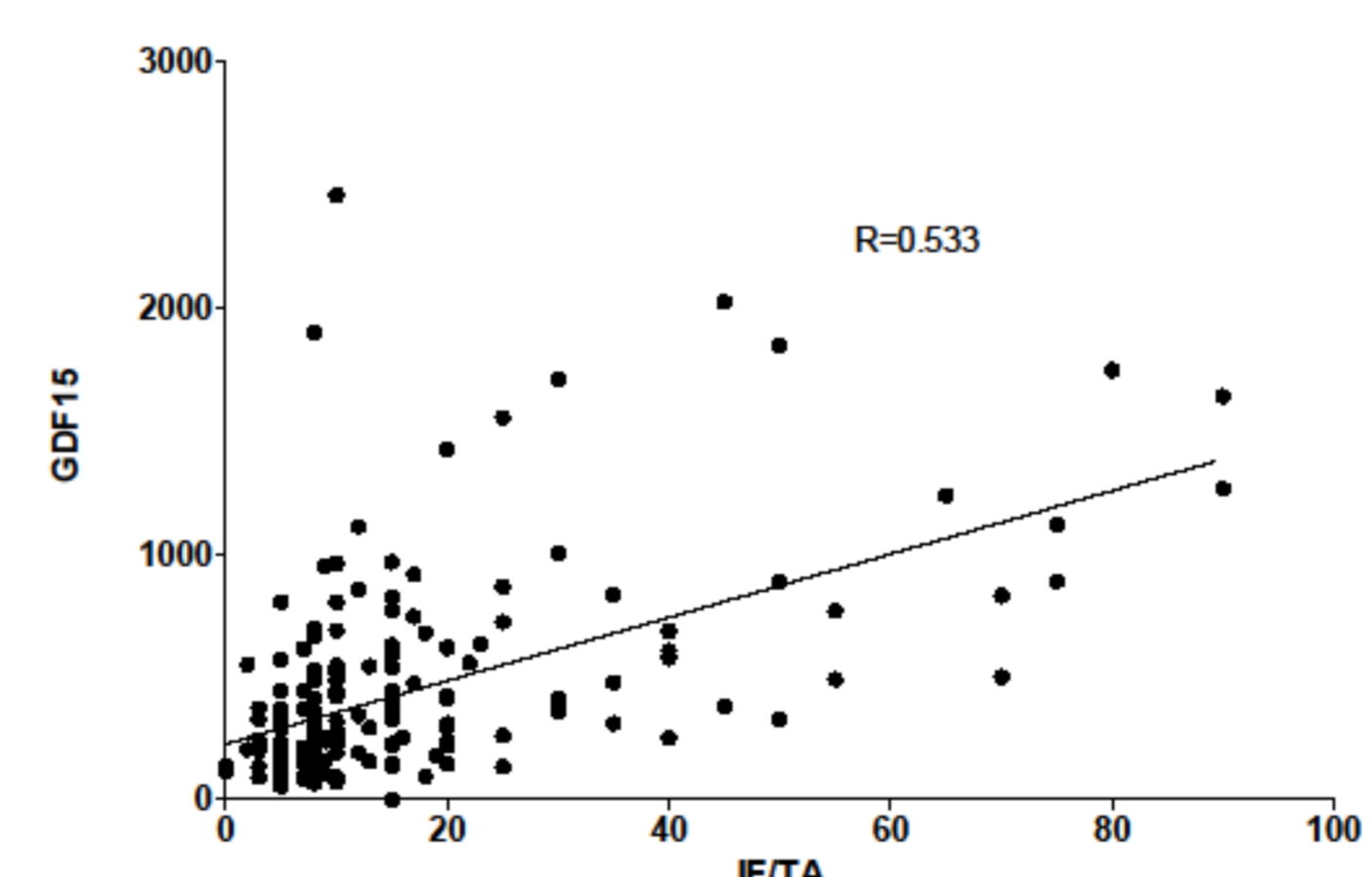


Figure 5. Receiver operation characteristic curve between GDF 15 and kidney prognosis. A: Serum growth differentiation factor 15 (GDF 15) level > 496.32 pg/mL showed 90% sensitivity and 72.9% specificity to predict the need for hemodialysis within 2 years. The area under curve (AUC) of GDF 15 was 0.8477 \pm 0.075. B: GDF 15 level > 490.4 pg/mL showed 63.64% sensitivity and 65% specificity to predict a decline in eGFR > 30 ml/min in 1 year.



Pearson's coefficient	IF/TA	p
BUN	0.532	< 0.001
Creatinine	0.602	< 0.001
eGFR	-0.626	< 0.001
UPCR	0.233	0.001
GDF 15	0.533	< 0.001

Figure 6. The correlation between interstitial fibrosis and tubular atrophy (IF/TA) and GDF 15. Interstitial fibrosis/tubular atrophy (IF/TA) and serum GDF 15 level were correlated (r, 0.533).

Pearson's coefficient	IF/TA	p
BUN	0.532	0.000
Creatinine	0.602	0.000
eGFR	-0.626	0.000
UPCR	0.233	0.001
GDF 15	0.533	0.000

Table 3. Correlation with interstitial fibrosis and tubular atrophy.

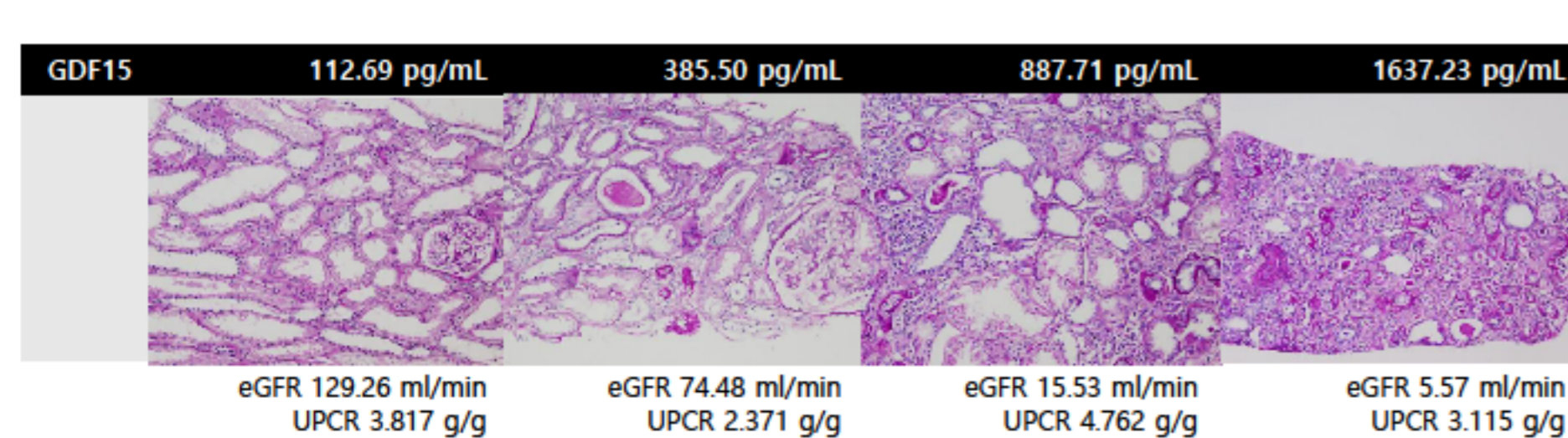


Figure 7. Representative serum GDF 15 and interstitial fibrosis/tubular atrophy (IF/TA) images. As the IF/TA percentage increased, serum GDF 15 level increased..

CONCLUSION :

Initial serum GDF 15 level associated with disease severity and prognostic marker in patients with IgA nephropathy.