Hyperphosphatemia: A Marker of Renal Injury and Outcome In Patients with Early Stage of Diabetic Nephropathy

Song Jiang, Yu Pan, Dandan Qiu, Yu An, Feng Xu, Yongchun Ge, Honglang Xie, Zhi-Hong Liu*

National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of medicine, Nanjing, China

Background:

- ☐ Hyperphosphatemia is a prognostic marker in late chronic kidney disease. Whether hyperphosphatemia may serve as a prognostic marker in early diabetic nephropathy (DN) with an eGFR≥60ml/min/1.73m2 is unknown.
- ☐ This study was aim to investigate the association of hyperphosphatemia with the renal outcome in type 2 diabetes (T2D) and DN patients, especially in the patients with eGFR≥60 ml/min per 1.73m2.

Methods:

- ☐ A total of 597 patients with T2D and DN were enrolled.
- ☐ Median 36 month follow-up were enrolled in this study. 404(69.4%) cases underwent renal biopsy.
- ☐ Renal outcomes were defined by progression to end-stage renal disease and doubling of serum creatinine.

Results:

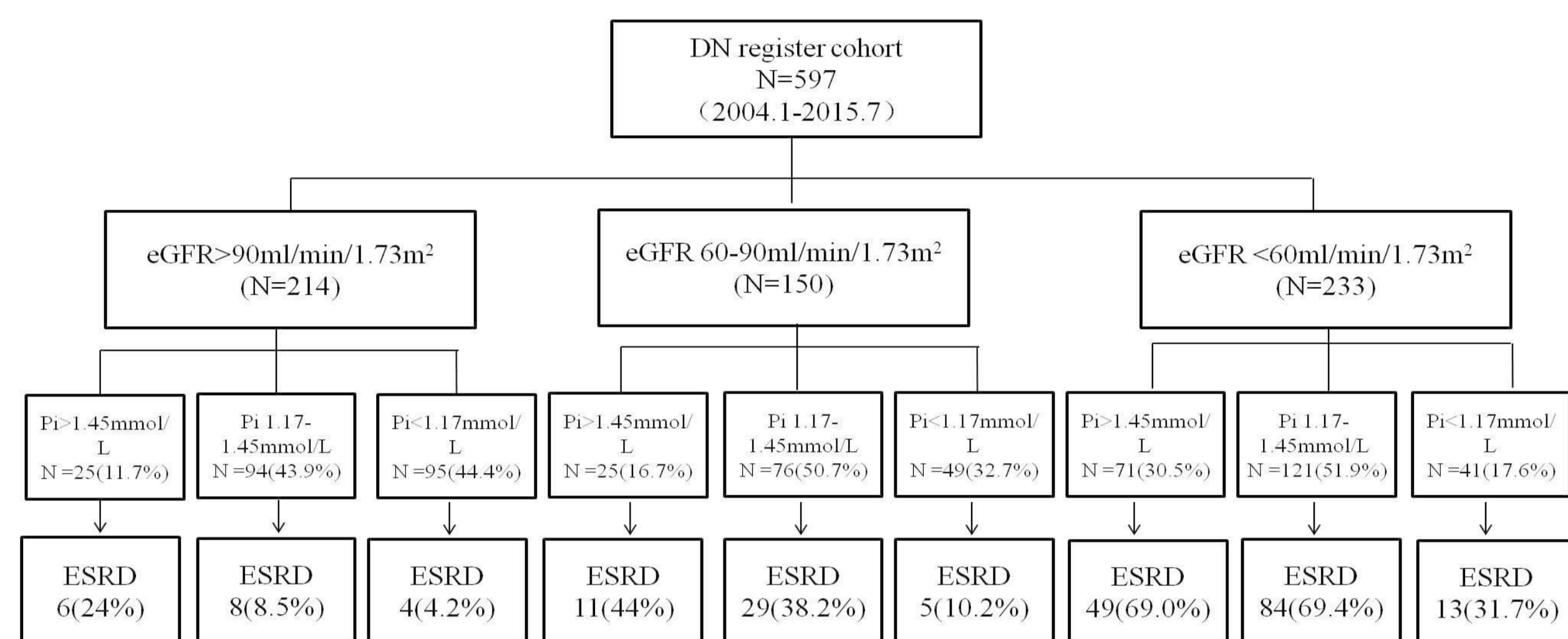### Table 1. Flow chart of Study

Figure 1. The incidence of hyperphosphatemia (>1.45mmol/L) in patients with DN .

A. The bar diagram show the incidence (%) of hyperphosphatemia in patients with DN. B. The scatterplot indicated the phosphate concentration.
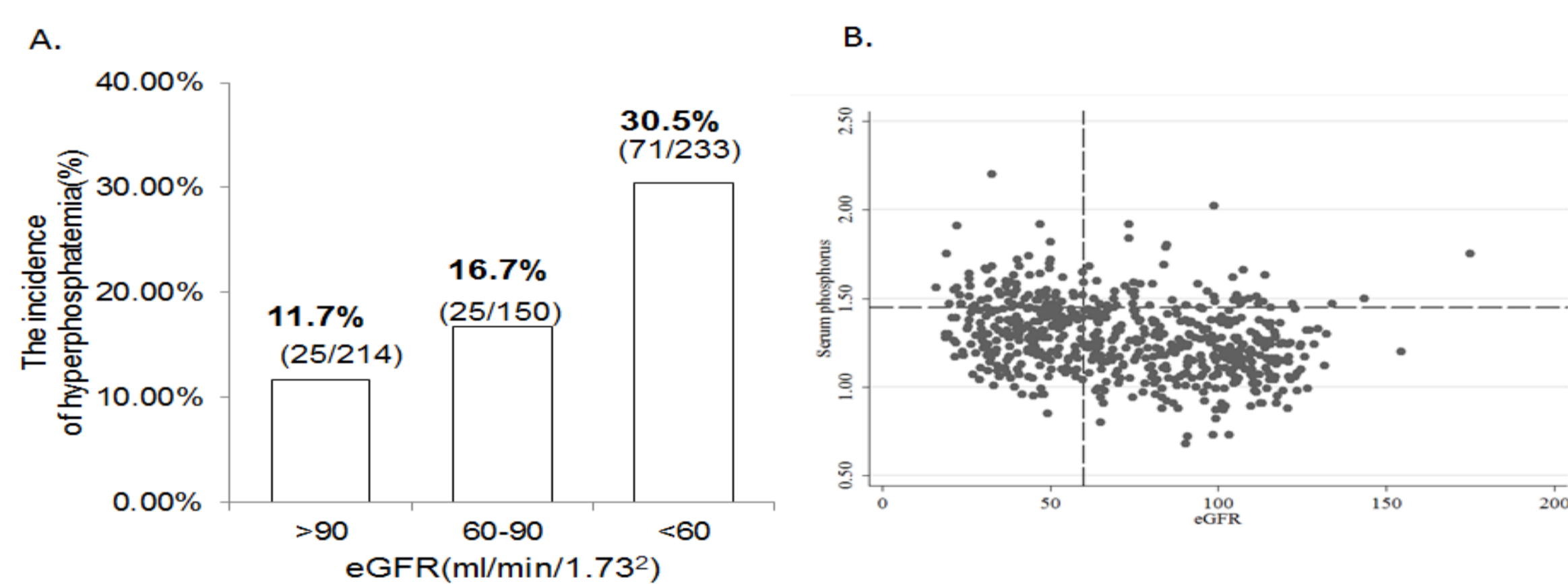

Table 3. Frequency, incidence rates, HRs, and 95% CIs for incident ESRD by quintile of serum levels of phosphate (n=597)

	Quintile of Serum Level of Phosphate (mmol/L)				
	25th(<1.17)		25th-75th (1.17-1.45)		75th (>1.45)
Participants (n)	185		291		121
Events	22		121		66
	25th (<1.17)	25th-75th (1.17-1.45)	P value for Trend[a]	75th (>1.45)	P value for Trend[a]
Model †1	1[ref]	3.94(95%CI 2.50-6.22)	p= 0.000	5.41(95%CI 3.33,8.77)	p= 0.000
2	1[ref]	3.98 (95%CI 2.52,6.27)	p= 0.000	5.65(95%CI 3.47,9.18)	p= 0.000
3	1[ref]	3.64(95%CI 2.05,6.46)	p= 0.000	5.25(95%CI 2.84, 9,69)	p= 0.000
4	1[ref]	3.67(95%CI 2.07, 6.52)	p= 0.000	5.36(95%CI 2.90, 9.92)	p= 0.001
5	1[ref]	3.92(95%CI 2.19, 7.02)	p= 0.000	6.60(95%CI 3.60, 12.16)	p= 0.000

† Models are as follows: model 1 is unadjusted (no covariates included in the model); model 2 is adjusted for age, sex; model 3 is adjusted for the variables in model 2 plus diabetes, systolic BP, HDL cholesterol, body mass index, proteinuria; model 4 is adjusted for variables in model 3 plus calcium and model 5 is adjusted for variables in model 4 plus eGFR-EPI.

Table 5. Pathologic features by quintile of serum levels of phosphate

eGFR	≥90ml/min/1.73m²			60-90 ml/min/1.73 m²			<60 ml/min/1.73m²		
phosphate	<1.17	>=1.45	P value	<1.17	>=1.45	P value	<1.17	>=1.45	P value
Glomerular Classification			0.578			0.327			0.519
I	23(32.8)	5(27.8)		5(17.2)	2(11.1)		0(0)	1(1.9)	
II(a+b)	34(48.5)	5(27.8)		14(58.2)	3(16.6)		8(46.3)	7(13.3)	
III	13(18.5)	8(44.4)		7(24.1)	11(61.1)		9(40.9)	33(63.4)	
IV	0(0)	0(0)		3(10.3)	2(11.1)		5(22.7)	11(21.1)	
IFTA			0.000			0.021			0.007
0	22(31.4)	2(11.1)		6(20.6)	0(0)		0(0)	0(0)	
1	43(61.4)	10(55.5)		19(65.5)	11(61.1)		13(59.1)	9(17.3)	
2	4(5.71)	6(33.3)		4(13.7)	5(27.7)		5(22.7)	15(28.8)	
3	1(1.42)	0(0)		0(0)	2(11.1)		4(18.2)	28(53.8)	
Interstitial Inflammation			0.055			0.007			0.08
0	27(38.5)	5(27.8)		9(31.0)	0(0)		1(4.5)	0(0)	
1	38(54.3)	10(55.5)		15(51.7)	12(66.6)		14(63.3)	16(30.7)	
2	5(7.14)	3(16.6)		5(17.2)	6(33.3)		7(31.8)	36(69.2)	

Table 2 Participant baseline clinical characteristics based on total serum phosphate concentration quartiles (n=597)

		serum phosphate			
	ALL	25th [<1.17]	25th-75th [1.17-1.45]	75th [>1.45]	p value
Participants * (n)	597	185	291	121	
Serum phosphate * (mmol/L)	1.27±0.20	1.050±0.09	1.30±0.80	1.57±0.12	0.000
Age* (yr)	49.43±9.34	50.22±8.05	49.58±9.29	47.87±11.23	0.094
Sex, male(%)	384(64.3)	135(73.0)	187(64.3)	62(51.2)	0.001
BMI * (kg/m²)	25.70±3.63	26.15±3.55	25.55±3.63	25.32±3.71	0.166
DM duration† (month)	84(27.75,156)	60(19.75,123)	96(33,144)	75(41.75,177)	0.000
SBP * (mmHg)	139.81±17.97	137.63±17.63	141.06±18.36	140.17±17.38	0.124
DBP * (mmHg)	83.30±9.79	82.30±9.34	83.81±9.65	83.60±10.69	0.242
Proteinuria† (g/24h)	1.42(0.61,3.47)	0.74(0.40,1.62)	1.55(0.69,3.57)	2.73(1.44,4.78)	0.000
Serum calcium* (mmol/L)	2.21±0.16	2.26±0.15	2.20±0.17	2.19±0.17	0.001
FBG * (mmol/L)	7.50±2.78	7.92±2.73	7.42±2.93	7.05±2.39	0.020
HbA1c* (%)	6.99±1.52	7.07±1.44	6.98±1.55	6.91±1.56	0.842
Cholesterol * (mmol/L)	5.54±1.88	5.13±1.45	5.58±2.02	6.07±1.97	0.000
Serum albumin * (g/L)	40.25±7.51	43.67±6.32	39.48±7.50	36.89±7.24	
eGFR * (ml/min per 1.73m2)	73.17±30.63	84.64±27.14	71.14±30.10	60.54±31.10	0.000

Figure 2. Kaplan–Meier curves of renal survival rate in patients with serum phosphate concentration quartiles.
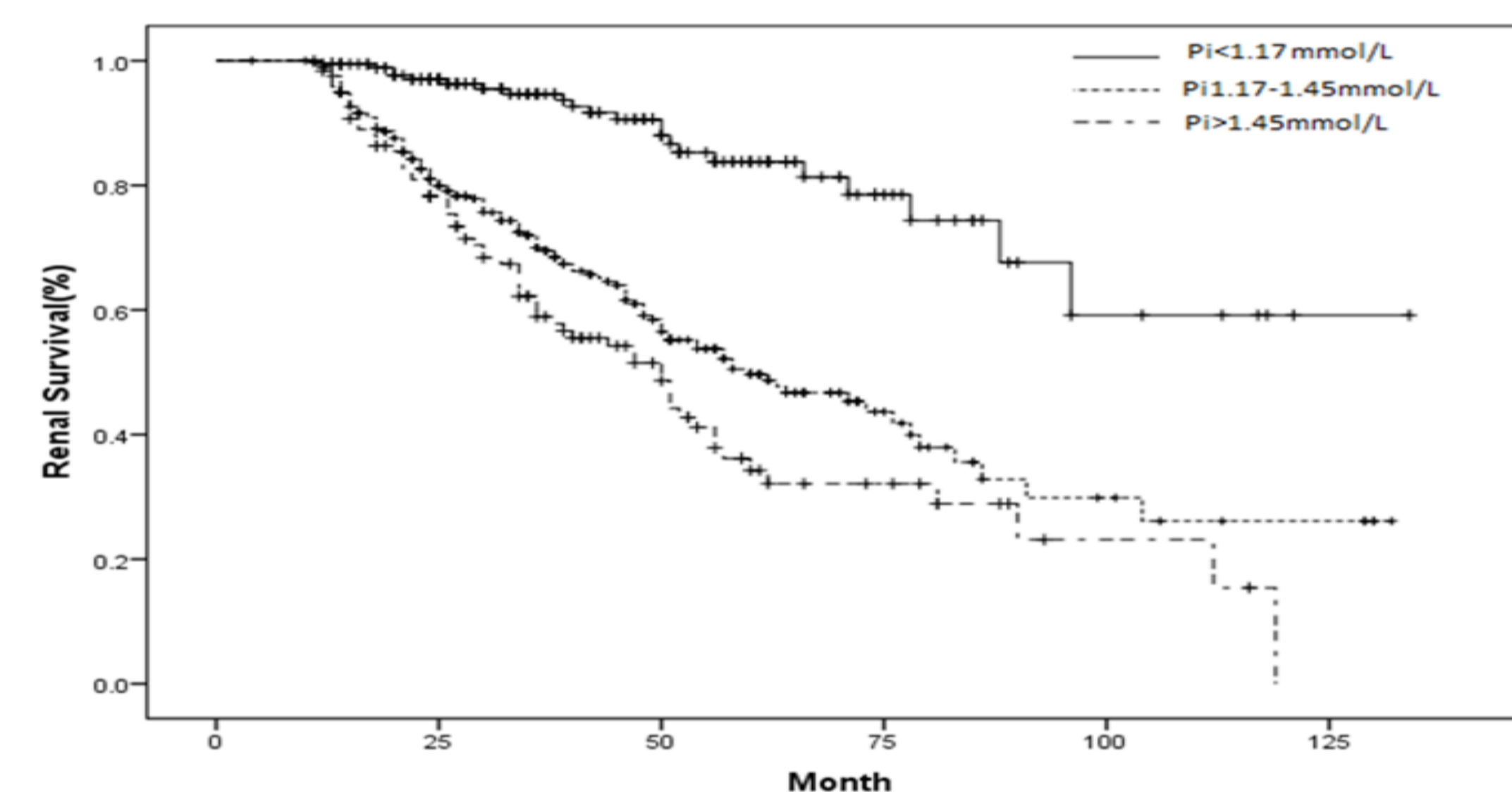

Table 4. HRs and 95% CIs for ESRD by quintile of serum levels of phosphate according to category of baseline kidney function (n=597)

eGFR	phosphate	Hazard ratio	P value
>90ml/min/1.73m²	<1.17	1[ref]	
	1.17-1.45	1.05(0.97,1.13)	P=0.221
	>1.45	1.26(1.00,1.58)	P=0.004
60-90ml/min/1.73m²	<1.17	1[ref]	
	1.17-1.45	1.45(1.19, 1.77)	P=0.000
	>1.45	1.60(1.12,2.30)	P=0.000
<60ml/min/1.73m²	<1.17	1[ref]	
	1.17-1.45	2.23(1.59,3.13)	P=0.000
	>1.45	2.20(1.47,3.30)	P=0.000

Model was adjusted for age, sex, BMI, blood pressure, proteinuria, eGFR.
eGFR, estimated glomerular filtration rate.

Figure 3. the relationship between Hyperphosphatemia and tubular injured marker, 24h proteinuria and eGFR. Hyperphosphatemia elevated the NGAL(A), NAG(B), RBP(C) level.

Conclusions:

- Our findings indicated serum phosphate >1.45mmol/L is an independent risk factor of ESRD in T2D with DN patients, especially in the patients with eGFR≥60 ml/min per 1.73m².
- In addition, our study provide clear evidence that baseline serum phosphate level is strongly associated with tubularinterstitial injury in DN patients.
- Hyperphosphatemia has potential to be a early prognostic marker for progression in DN patients.