

# Predictors of Faster Progression in Chronic Kidney Disease

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**Objective:** To study the factors associated with faster progression in chronic kidney disease.

**Material and Method:** A cohort study of CKD stage 2 to 4 patients of the CKD clinic at Thungsong Hospital between 2008 and 2011 was done. At the end of the study, the patients were classified as faster or slower group according to rate of GFR decline. Apart from descriptive analysis, univariate and multivariate analysis were used to perform correlations analysis between rate of eGFR decline and each variable.

**Results:** Two hundred three patients were enrolled and followed-up for three years. The average rate of eGFR decline (SD) was 2.25 (3.65) mL/min/1.73 m<sup>2</sup> per year. In univariate analysis, factors that correlated with rate of eGFR decline were systolic blood pressure ( $r = 0.155$ ,  $p = 0.027$ ), serum albumin ( $r = -0.172$ ,  $p = 0.042$ ), serum bicarbonate ( $r = -0.158$ ,  $p = 0.046$ ), age ( $r = -0.157$ ,  $p = 0.025$ ), and proteinuria ( $r = 0.276$ ,  $p < 0.001$ ). Furthermore, logistic regression analysis revealed the strong predictors of faster progression were systolic blood pressure (OR = 1.025, 95% CI = 1.003-1.047,  $p = 0.025$ ) and particularly, proteinuria (OR = 1.887, 95% CI = 1.325-2.688,  $p < 0.001$ ).

**Conclusion:** Among the factors that associated with faster eGFR decline, only systolic blood pressure and especially, proteinuria were powerful predictors of faster progression in chronic kidney disease.

**Keywords:** Predictors, Faster progression, Chronic kidney disease (CKD)

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In many parts of the world, end-stage renal disease (ESRD) has a profound effect on morbidity, mortality, and quality of life, and imposes a substantial burden on health care expenditure<sup>(1)</sup>. Most patients with chronic kidney disease (CKD) stage 3 to 5 progress perpetually to ESRD. The change in global approach to CKD from treatment of ESRD to much more aggressive primary and secondary prevention is therefore imperative<sup>(2)</sup>.

The progressive decline has been ascribed to variety of mechanisms, such as failure to resolve the initial injury, and onset of self-perpetuating injury, ultimately lead to the typical pathologic features of the end stage kidney and kidney failure<sup>(3)</sup>. Although many studies in western countries showed some prognostic factors that obviously associated with rapid decline in kidney function, many factors were even equivocal<sup>(4-8)</sup>.

In Southeast Asia, especially in Thailand, according to the Thai SEEK study, the CKD prevalence in Thai population was 17.5%, with some geographical variation. Among predictors of CKD, exposure to

traditional medicines seemed to be important<sup>(9)</sup>. Nevertheless, *Parkia speciosa*, known as sator or sataw in Thailand, is a plant abundantly found in Southern Thailand and Malaysia. *Parkia speciosa* seeds have always been a popular ingredient in cooking due to its strong and pungent odor; it has been widely consumed by people in this region. Besides culinary uses, it is reported to have beneficial effects on health<sup>(10,11)</sup>.

The other CKD studies in Thailand were mainly examined on the aspect of prevalence<sup>(12,13)</sup>. However, the study of the risk factors for development of decrease kidney function in Thai population, reported in 2005, mostly confined to patients with normal kidney function or early stage of CKD<sup>(14)</sup>. Hence, the objective of the present study was to comprehensively study the factors (predictors) associated with faster progression in various stages of chronic kidney disease in Thai population living in the Southern region.

## Material and Method

### Participant and study design

The consecutive, CKD stage 2 to 4 patients as K/DOQI 2002 definition who attended the CKD clinic in Thungsong Hospital, a community hospital in Nakhon Si Thammarat province, between January and

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December 2008 were included in this prospective cohort study, and followed until December 2011. The patients with serious systemic disease, refractory congestive heart failure, decompensated cirrhosis, or advanced stage cancer were excluded. The dependent variable (Outcome) of the present study was the rate of eGFR decline. The independent variables (Predictors) that possibly might be associated with faster progression, which to be rigorously examined in the present study were the patients' baseline demographic, clinical, and laboratory data. The permission to conduct the study was granted from the Thungsong Hospital Ethical Committee.

### Measurement and definitions

Age, gender, body mass index (BMI), tobacco use, diabetes, baseline estimated GFR (eGFR), mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, Hemoglobin (Hb), serum albumin, serum bicarbonate, and urine protein dipstick values were thoroughly recorded. The results of urine protein dipstick test reported by auto-analyzer machine (product of Dirui Industrial Company limited) were designated as negative, trace, 1+, 2+, and 3+, which corresponded to concentration of 0, 15, 30, 100, and 300 mg/dL or more, respectively. Serum creatinine, which was collected every four to six months was measured by alkaline picrate method (Modified Jaffe' reaction) with GM-800 automated analyzer. The eGFR was calculated using the Abbreviated MDRD study equation:  $eGFR = 186 \times (SCr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female})$ . Faster progression defined as eGFR declining rate  $\geq 4$  mL/min/1.73 m<sup>2</sup> per year, and slower progression defined as eGFR declining rate less than 4 mL/min/1.73 m<sup>2</sup> per year, which corresponded to K/DOQI-CKD 2002 guideline.

### Statistical analysis

Apart from descriptive analysis, the SPSS Statistics 16.0 program was used to compute One-Sample Kolmogorov-Smirnov test for distribution testing, Independent-Samples t-test for mean comparing of normal distribution variables, non-parametric Mann-Whitney U test for comparing of non-normal distribution variables. Importantly, bivariate Pearson and non-parametric Spearman's rho analysis was performed to examine correlation in appropriate variables. In addition, log transformation was applied to make data (baseline eGFR) more normally distributed before correlation analysis.

Finally, multivariate analysis by binary logistic regression models were meaningfully used to compute predictive values of those that positive correlation in the former univariate analysis.

### Results

Two hundred ten patients were registered between January 1 and December 31, 2008. Among those, only 203 cases were enrolled in the study after exclusion of seven cases of serious systemic disease such as refractory congestive heart failure (3 cases), decompensated cirrhosis (2 cases), or advanced stage cancer (2 cases). The overall median (range) follow-up was 3.0 (1.0-3.3) years. One hundred seventy seven (87%), 11 (6%), and 15 (7%) patients were followed for 3, 2, and 1 year, respectively (Fig. 1). Among those (n = 11) with 2-year follow-up, eight and three patients were lost and stopped follow-up to receive renal replacement therapy, respectively. Among those (n = 15) with 1-year follow-up, nine, four, and two patients were lost, stopped follow-up to receive renal replacement therapy, and died, respectively.

The mean age of the patients was  $65.77 \pm 13.25$  years, with 110 (54%) male patients. At baseline, the median (range) eGFR was 34.90 (15.12-88.42) mL/min/1.73 m<sup>2</sup>. Among those with diabetes, 72.40% of overall, mean HbA1c was  $5.87 \pm 2.06\%$ . Thirty-six (17.70%), 88 (43.30%), and 79 (38.90%) patients were categorized as CKD stage 2, 3, and 4, respectively. One hundred thirty three (66%), 45 (22%), and 24 (12%) patients were non-smoker, ex-smoker, and smoker, respectively. The mean systolic blood pressure, diastolic blood pressure, and mean arterial pressure were  $137.41 \pm 14.73$ ,

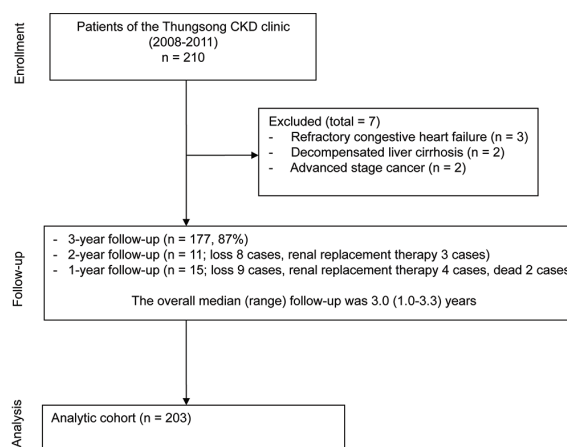


Fig. 1 Flowchart of the patients from enrollment to analysis.

77.96±9.77, and 97.75±11.31 mmHg, respectively. The dipsticks proteinuria, quantitative test was negative, trace, 1+, 2+, and 3+ in 47 (23.1%), 50 (24.40%), 44 (21.90%), 33 (16.20%), and 29 (14.40%) patients, respectively. The mean hemoglobin, bicarbonate, and serum albumin were 11.85±1.88 g/dL, 25.88±4.25 mEq/L, and 4.5±0.55 g/dL, respectively. The overall demographic and clinical characteristics of the study population at baseline were shown in Table 1.

At the end of the study, the mean eGFR decline in all cases was 2.25±3.65 mL/min/1.73 m<sup>2</sup> per year. Fifty-four (26.6%) and 149 (73.4%) patients were classified in faster and slower progression, respectively. The mean eGFR decline in the faster and the slower group was 7.03±2.52 and 0.52±2.13 mL/min/1.73 m<sup>2</sup> per year, respectively. The difference

**Table 1.** Demographic and clinical characteristics of the study population at baseline (n = 203)

Variables	Values
Age, years	65.77±13.25
Gender, male (%)	110 (54.2)
Body mass index, kg/m <sup>2</sup>	24.69±4.20
Diabetes, %	147 (72.4)
eGFR, mL/min/1.73 m <sup>2</sup>	34.90 (15.12-88.42)
CKD stage, %	
2	36 (17.7)
3	88 (43.4)
4	79 (38.9)
Tobacco use, %	
Non smoker	99 (66.0)
Ex-smoker	33 (22.0)
Smoker	18 (12.0)
Systolic blood pressure, mm Hg	137.41±14.73
Diastolic blood pressure, mm Hg	77.96±9.77
Mean arterial pressure, mm Hg	97.75±11.31
HbA1c, %	5.87±2.06
Dipsticks proteinuria, %	
Negative	37 (23.1)
Trace	39 (24.4)
1+	35 (21.9)
2+	26 (16.2)
3+	23 (14.4)
Hb, g/dL	11.85±1.88
CO <sub>2</sub> (SD), mEq/L	25.88±4.25
Serum albumin, g/dL	4.50±0.55

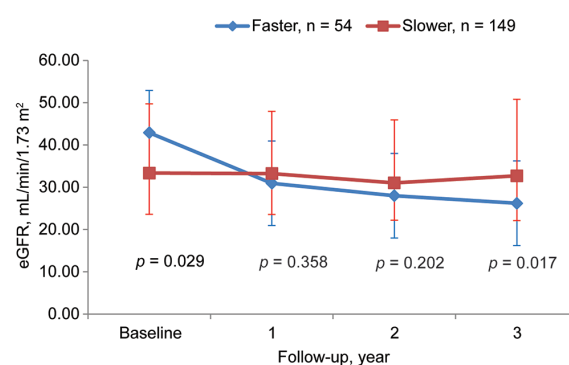
CKD = chronic kidney disease

Values are expressed as n (%), mean ± SD or median (range)

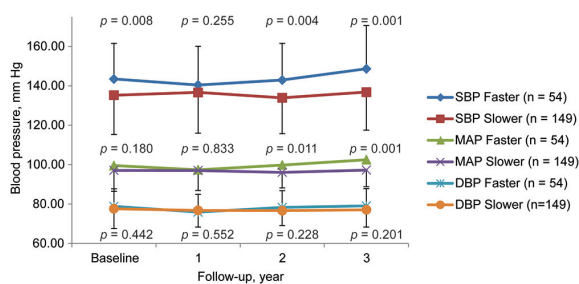
HbA1c represented only in diabetes group

of the mean eGFR of the faster compared to the slower group was significantly higher and lower at the baseline ( $p = 0.029$ ) and the end of study ( $p = 0.017$ ), respectively (Fig. 2).

Systolic blood pressure was significantly higher in the faster progression group at baseline ( $p = 0.008$ ), 2-year ( $p = 0.004$ ), and 3-year ( $p = 0.001$ ) follow-up, compared to the slower group. Mean arterial pressure was only significantly higher in the faster group at 2-year ( $p = 0.011$ ) and 3-year ( $p = 0.001$ ) follow-up; however, no significant difference in diastolic blood pressure between the two groups (Fig. 3).



**Fig. 2** Estimated glomerular filtration rate (eGFR) from baseline to selected follow-up time of faster (◆) and slower (■) groups. The faster; n = 54, 52, 46 and 43 at baseline, 1-, 2- and 3-year follow-up, respectively. The slower; n = 149, 148, 142 and 134 at baseline, 1-, 2- and 3-year follow-up, respectively. Values expressed as median with 25<sup>th</sup> and 75<sup>th</sup> percentiles in error bars.



**Fig. 3** Systolic blood pressure (SBP), mean arterial pressure (MAP) and diastolic blood pressure (DBP) from baseline to selected follow-up time of faster (◆, ▲ and \* for SBP, MAP and DBP, respectively) and slower (■, × and ●, respectively) groups. The Faster; n = 54, 52, 46 and 43 at baseline, 1-, 2- and 3-year follow-up, respectively. The Slower; n = 149, 148, 142 and 134 at baseline, 1-, 2- and 3-year follow-up, respectively. Values expressed as mean and SD in error bars.

**Table 2.** Correlation coefficients (r) for each variable to eGFR decline

Variables	eGFR decline		
	n	r	p-value
Age	203	-0.157	0.025*
Gender	203	0.063 <sup>+</sup>	0.370
BMI	163	0.140	0.074
Tobacco use	150	-0.117 <sup>+</sup>	0.154
Diabetes	203	0.064 <sup>+</sup>	0.362
Baseline eGFR	203	0.114 <sup>#</sup>	0.105
MAP	203	0.123	0.079
SBP	203	0.155	0.027*
DBP	203	0.090	0.201
HbA1c	101	0.117	0.246
Hb	195	-0.131	0.068
Serum albumin	141	-0.172	0.042*
Serum bicarbonate	161	-0.158	0.046*
Urine protein dipstick	160	0.276 <sup>+</sup>	<0.001*

r = correlation coefficients; eGFR = estimated glomerular filtration rate; MAP = mean arterial pressure; DBP = diastolic blood pressure; BMI = body mass index; Hb = hemoglobin  
<sup>+</sup> Nonparametric Spearman's rho correlation coefficient  
<sup>#</sup> Correlation after log-transformation

In univariate analysis, factors that correlated with rate of eGFR decline were SBP ( $r = 0.155$ ,  $p = 0.027$ ), serum albumin ( $r = -0.172$ ,  $p = 0.042$ ), serum bicarbonate ( $r = -0.158$ ,  $p = 0.046$ ), age ( $r = -0.157$ ,  $p = 0.025$ ) and proteinuria ( $r = 0.276$ ,  $p < 0.001$ ). Whereas baseline eGFR, gender, BMI, tobacco use, diabetes, mean arterial pressure, diastolic blood pressure, HbA1c, and hemoglobin were not statistically significant correlated with eGFR decline (Table 2).

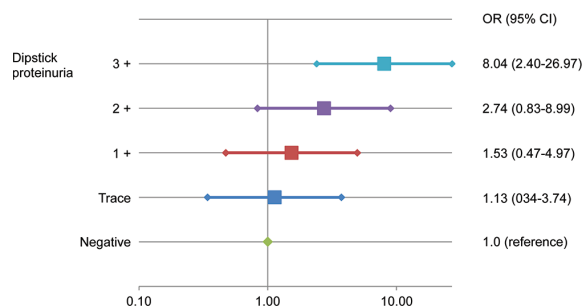
**Table 3.** Predictive values for faster<sup>+</sup> progression in binary logistic regression models

Variables	Model 1			Model 2		
	p-value	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI
Age	0.343	0.970	0.929-1.026	-	-	-
Serum albumin	0.463	0.962	0.259-1.848	-	-	-
Serum bicarbonate	0.437	1.064	0.911-1.242	-	-	-
SBP	0.124	1.035	0.991-1.081	0.025*	1.025	1.003-1.047
Proteinuria <sup>#</sup>	0.048*	1.972	1.005-3.871	<0.001*	1.887	1.325-2.688

OR = odd ratio or Exp(B) of output data in SPSS; CI = confidence interval for Exp(B); SBP = systolic blood pressure  
 Overall percentage correct = 82.9 and 76.9 in Model 1 and 2, respectively

<sup>#</sup> After transform data from negative, trace, 1+, 2+ and 3+ to 0, 15, 30, 100 and 300 mg/dL, respectively

<sup>+</sup> eGFR declining rate  $\geq 4$  mL/min/1.73 m<sup>2</sup> per year



**Fig. 4** Unadjusted odds ratio (OR) in log [10] scale and 95% confidence interval to measure effect of each values of urine protein dipstick test for predicting the faster progression; Lower 95% confidence limit (the first small head), observed odds ratio (the large square head) and upper 95% confidence limit (the last small head).

Additionally, as shown in Fig. 4, a directly proportional relationship was evident between dipstick proteinuria and rate of eGFR decline. Obviously, compared with those who had urine dipstick negative, those with urine dipstick 3+ were likely to demonstrate faster progression (unadjusted OR = 8.04, 95% CI 2.40 to 26.97;  $p = 0.001$ ).

In multivariate analysis by Binary Logistic regression; the Model 1, in which overall percent correct prediction was 82.9%, we found that only proteinuria had statistically significant predictive value for faster progression ( $p = 0.048$ , adjusted OR = 1.972, 95% CI 1.005-3.871); the Model 2, additionally, in which overall percent correct prediction was 76.9%, it showed that both proteinuria and systolic blood pressure were the remarkable predictors ( $p < 0.001$  and  $p = 0.025$ , adjusted OR = 1.887 and 1.025, 95% CI = 1.325-2.688 and 1.003-1.047, respectively) (Table 3).

## Discussion

In the authors' knowledge, this is the first study in South East Asia that examined many different traditional-progression-factors or markers<sup>(15)</sup> in consecutively CKD-clinic-based setting. In summary, based on univariate analysis, the present study showed that younger age, systolic blood pressure, proteinuria, low serum albumin, and low serum bicarbonate were the predictors of progression. However, multivariate analysis revealed that only systolic blood pressure and proteinuria were powerful predictors of faster progression. The present study showed the average of eGFR decline in Thai-CKD patients was  $2.25 \pm 3.65$  mL/min/1.73 m<sup>2</sup> per year, which has never been reported before. The limitation of the present study was that the data were primarily collected in clinical service, not academically for research purpose.

The present finding that younger age as a predictor of progression in univariate analysis was consistent with O'Hare et al<sup>(5)</sup>, and Leehey et al<sup>(16)</sup>. The loss of eGFR in old age is believed to occur as part of "normal aging" rather than as a "disease process"<sup>(17)</sup>. Low eGFR in older might be a better predictor of "global" health outcomes than a more specific renal outcome. In addition, the abbreviated MDRD study equation used to estimate GFR has not been validated across the range of age and eGFR levels examined here<sup>(5)</sup>. On the contrary, Rossing et al and Hallan et al had reported that older age was directly associated with eGFR decline<sup>(18,19)</sup>.

Nearly all univariate analysis and some multivariate analysis in most studies showed systolic blood pressure as a predictor of the progression similar to the present study<sup>(16,18-20)</sup>. The model of CKD progression described by Taal and Brenner, elevated systemic blood pressure transmitted to the glomerulus would contribute to glomerular hypertension and thus accelerate glomerular damage<sup>(21)</sup>. Unanimously, the authors' finding and almost all other studies revealed that proteinuria was the obviously influential progression factor<sup>(6)</sup>. Proteinuria is usually considered as a marker of the extent of glomerular damage, but studies in various experimental animal models suggest that proteinuria may contribute to glomerular and tubulointerstitial lesion<sup>(22)</sup>, and play a role of renal scarring<sup>(23)</sup>.

Serum albumin level, generally regarded as a marker of nutritional status, may be reduced due to proteinuria, inflammation or metabolic acidosis<sup>(24)</sup>. Consistent with the present study, univariate analysis

from MDRD study found correlation between higher baseline serum albumin and slower subsequent rate of GFR decline<sup>(4)</sup>. Furthermore, the two-interesting studies confirmed that the predictive value of hypoalbuminemia and proteinuria, indicating that it is not just acting as a marker of albuminuria<sup>(16,25)</sup>.

Low serum bicarbonate as a predictor of progression was consistent with many studies<sup>(16,20,26,27)</sup>. The mechanism(s) cause the decline in GFR by metabolic acidosis was revealed in rats by Nath et al, in which provided evidence of association between acidosis-induced stimulation of renal ammonia production and progressive tubulointerstitial injury by activated the complement cascade<sup>(28)</sup>. Others have proposed that the stimulation of new bicarbonate production in the kidney alkalinize medullar area encourages precipitation of calcium in the kidney causes renal injury<sup>(29)</sup>.

In addition, as stated by the Thai SEEK study, the prevalence of CKD in the Southern region was lower as compared to Bangkok, Northeastern, and Northern regions. Many reasons might be explained the variation of CKD prevalence by region such as higher prevalence of diabetes in Bangkok, higher prevalence of kidney stone in the Northeastern and Northern regions<sup>(9)</sup>. Many studies showed beneficial effects on health of *Parkia speciosa*<sup>(10,11,30,31)</sup>, which was widely consumed by people in southern Thailand, including participants in the present study. However, it could not extrapolate that *Parkia speciosa* might perhaps play a role in the lower prevalence of CKD in the Southern region, or might possibly be a factor that had influenced GFR decline. Further studies must be needed to document whether the *Parkia speciosa* has any effect on renal function.

Finally, the present study could be used in CKD patients applicable in most hospitals in Thailand, because of the broad range of eGFR and various causes of CKD of the participants in the present study. However, the weakness of the present study was that it was single-center-based and had small sample size.

## Conclusion

The authors concluded that among the factors, systolic blood pressure, low serum albumin, low serum bicarbonate, younger age, and proteinuria, that were statistically significant associated with faster eGFR decline, only the systolic blood pressure and proteinuria were the powerful predictors of faster progression in chronic kidney disease.

### What is already known on this topic?

Although in many western countries, some factors were established as the predictors of faster progression in chronic kidney disease, many factors were still ambiguous.

In South-East Asia, no study comprehensively revealed the factors associated with rapid decline of renal function in CKD patients.

### What this study adds?

In Thai CKD patients, which might be extrapolated to South East Asian populations, the mean (SD) eGFR decline was 2.25 (3.65) mL/min/1.73 m<sup>2</sup> per year. Most predictors of faster progression were generally in harmony with other parts of the world.

Among the predictors of faster progression, proteinuria had the most potency.

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### Potential conflicts of interest

None.

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## ปัจจัยที่เป็นตัวทำนายไตเสื่อมเร็วในผู้ป่วยโรคไตเรื้อรัง

ธีรพล สุขมาก, ศุภานัน สุขมาก

วัตถุประสงค์: เพื่อศึกษาปัจจัยที่สัมพันธ์กับไตเสื่อมการทำงานเร็วในผู้ป่วยโรคไตเรื้อรัง

วัสดุและวิธีการ: เป็นการศึกษาวิเคราะห์ชนิดไปข้างหน้า ในผู้ป่วยโรคไตเรื้อรังระยะที่ 2 ถึง 4 ที่เข้ารับบริการที่คลินิกโรคไตเรื้อรัง โรงพยาบาลทุ่งสง ในระหว่างปี พ.ศ. 2551 ถึง พ.ศ. 2554 โดยหลังจากสิ้นสุดการศึกษาจะแบ่งผู้ป่วยออกเป็นสองกลุ่มคือ กลุ่มไตเสื่อมช้าและไตเสื่อมเร็ว นอกเหนือจากสถิติเชิงพรรณนาแล้ว ยังใช้ *univariate analysis* และ *multivariate analysis* ในการหาความสัมพันธ์ของตัวแปรที่เกี่ยวข้อง

ผลการศึกษา: ผู้ป่วยที่ศึกษาจำนวน 203 ราย และติดตามเป็นเวลา 3 ปี อัตราเฉลี่ยการลดลงของการทำงานของไตเท่ากับ 2.25 มล./นาที/1.73 ตารางเมตร ต่อปี ในการศึกษาแบบ *univariate analysis* พบว่าปัจจัยที่สัมพันธ์กับไตเสื่อมเร็วได้แก่ ความดันโลหิตซิสโตลิก ( $r = 0.155, p = 0.027$ ), อัลบูมินในเลือด ( $r = -0.172, p = 0.042$ ), ไบคาร์บอเนตในเลือด ( $r = -0.158, p = 0.046$ ), อายุ ( $r = -0.157, p = 0.025$ ) และ โปรตีนในปัสสาวะ ( $r = 0.276, p < 0.001$ ) และจากการศึกษาโดยใช้ *logistic regression analysis* เพิ่มเติม พบว่ามีเพียงความดันโลหิตซิสโตลิก และโดยเฉพาะอย่างยิ่ง ภาวะโปรตีนในปัสสาวะที่เป็นตัวทำนายที่ชัดเจนเกี่ยวกับไตเสื่อมเร็วในผู้ป่วยโรคไตเรื้อรัง

สรุป: ในบรรดาปัจจัยที่พบว่าสัมพันธ์กับไตเสื่อมเร็ว นั้น พบว่าเฉพาะความดันโลหิตซิสโตลิก และโดยเฉพาะอย่างยิ่ง ภาวะโปรตีนในปัสสาวะเป็นตัวทำนายไตเสื่อมเร็วในผู้ป่วยโรคไตเรื้อรัง

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