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THE IMPACT OF HYPERURICEMIA ON THE RENAL SURVIVAL IN THE MALAYSIAN CKD POPULATION

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BACKGROUND
Chronic kidney disease (CKD) has a global prevalence of 10-15%. Studies have reported an association of hyperuricemia with the progression of CKD, but their conclusions are often contradictory. In this study, we aim to analyse the association between serum uric acid with rapid renal function decline in a tertiary centre in Asia.

METHODS
This is a retrospective study conducted in a tertiary nephrology clinic. A total of 416 patients were recruited and followed up from 2007 until June 2019. Data were extracted from the electronic health information system. This research has received the necessary ethical clearance from the National Medical Research & Ethics Committee. The Kaplan-Meier survival curve was used to analyse the renal outcomes, which consisted of 50% deterioration of GFR, doubling of the baseline serum creatinine, initiation of kidney replacement therapy (KRT) and mortality. Correlation statistical analysis was carried out to further determine the relationship of renal outcome with serum uric acid.

RESULTS
There is a significant association between hyperuricemia with GFR, serum creatinine and proteinuria. A Kaplan Meier analysis showed a significant association between serum uric acid and the various kidney outcomes, namely the halving of glomerular filtration rate ($p = 0.057$) and mortality ($p = 0.005$) but not significant with regards to the need for initiation of kidney replacement therapy or doubling of serum creatinine (57% decline in glomerular filtration rate).

CONCLUSION
Our study showed hyperuricemia is associated with worsening renal outcomes. Based on our data, we postulate there may be a certain threshold point of uric acid-induced kidney damage which is irreversible. A larger multicentre prospective study is warranted to validate this finding and to study the optimal time to start a uric acid-lowering agent.

KEYWORD
Causative roles, hyperuricemia, mortality, kidney replacement therapy, renal deterioration

INTRODUCTION
Elevated serum uric acid level levels are associated with increased risks of onset and progression of chronic kidney disease and end-stage kidney disease (ESKD) [1-2]. Observational studies have shown some association between serum uric acid level and various outcomes, including albuminuria [3], the onset of chronic kidney disease (CKD) [4-5], progression to ESKD [6], cardiovascular events, and death [7]. There is also an ongoing debate on the efficacy of uric acid-lowering agents on the progression of CKD. Recently, CKD-FIX and PERL studies reported that uric acid-lowering agents i.e., allopurinol and febuxostat did not provide any significant reduction of renal events in treating hyperuricemia in patients with CKD. Serum uric acid level increases progressively with worsening kidney function as a result of reduced excretion, making it difficult to assess its causative role in CKD progression or its predictive value in predicting rapid renal decline [8-9]. Therefore, the present study aims to elucidate whether serum uric acid affects renal decline.

METHODOLOGY
This retrospective observational cohort study was conducted in a tertiary nephrology centre in Malaysia. We analysed 416 CKD patients out of 458 patients with existing primary renal disease, renal transplants with underlying comorbidities, i.e. diabetes mellitus, hypertension, primary heart disease, cardiovascular disease, hyperlipidaemia and gout who attended the nephrology clinic between January 2007- June 2019. They were considered eligible if they had a baseline serum creatinine measurement and eGFR less than 90 mL/min with or without proteinuria.

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The Cockcroft and Gault formula (CG) equation was chosen as the study equation for GFR measurement [10]. Proteinuria was classified by quantitative measurements of 24-h urine protein. The uric acid level of (> 416 µmol/L = 6.99 mg/dl) was classified as high in our study. This study was approved by the National Medical Research & Ethics Committee with the registration of the number of NMRR-18-866-41231.

Outcome

Primary outcome:

We wish to identify the association of hyperuricemia with renal outcome and mortality. To account for nonspecific variations, a 50% eGFR reduction, doubling in serum creatinine and initiation of kidney replacement therapy (KRT) are the renal outcomes in our study.

Secondary outcome:

We wish to determine the possible relationship of hyperuricemia with renal outcomes. To account for nonspecific variations, estimated glomerular filtration rate (eGFR), serum creatinine and proteinuria.

Statistical analysis

Descriptive Measures

Quantitative variables are reported as mean ± SD or median and range, depending on the distribution. Absolute and relative frequencies were used for categorical variables. Under the assumption of an annual decline in eGFR of 3 ml per minute per 1.73 m2 [11], an initial enrolment of 458 participants before applying exclusion and inclusion criterion, with an adjusted loss of follow-up of 10% would provide a 80% power to detect a 20% decline in GFR deterioration overe 2 years of follow-up [12-13].

Outcome Analysis

Bivariate analysis was done to analyse the relationship between the level of serum uric acid with renal outcomes (GFR level, serum creatinine and proteinuria). Meanwhile, Kaplan Meier analysis was performed to analyse the survival rate of hyperuricemia with renal outcomes, to account for nonspecific variations, a 50% eGFR reduction, doubling in serum creatinine and initiation of KRT.

RESULT

Demographic data, baseline laboratory characteristic data of the 416 subjects are reported in Table 1.

PATIENT ENROLMENT AND BASELINE CHARACTERISTICS

January 2007 to June 2019, a total of 416 patients out of 458 patients (with the 10% drop out based on criterion) were recruited to this study with a minimum follow up of more than 6 months. The majority of the patient were Male (76.5%), Malay (63.5%), age more than 45 years old (82.7%), CKD stage 3 (36.4%), with underlying comorbidities i.e. hypertension and diabetes (99.3% and 59.1%). The mean (±SD) GFR was 51.84±33.75 ml per minute per 1.73 m2, the serum uric acid level more than 416 µmol/L (74.5%) and 24 h total urine protein more than 0.15 g/L (43.3%) (Table 1).

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Demographic baseline	%(n)	Mean ± SD	*Normal UA*	*Hyperuricemia*	X^2
Gender			***n=106***	***n=310***	
Male	55.3 (230)		23.5	76.5	
Female	44.7 (186)		28	72	0.297
Race					
Malay	63.5 (264)		23.5	76.5	
Chinese	26 (108)		31.5	68.5	
Indian	9.6 (40)		20	80	
Others	4 (4)		50	50	
BMI					
Underweight	2.9 (12)		66.7	33.3	
Normal	33.2 (138)		29	71	0.003
Overweight	40.4 (168)	26.12±4.42	22.6	77.4	
Obese	23.6 (98)		20.4	79.6	
Height		159.68±9.24			
Weight		68.27±13.69			
Age					
< 45 years old	17.3 (72)				
> 45 years old	82.7 (344)	61.32±14.48			

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eGFR Total Mean (Overall)					
Stage 1	14.9 (62)		38.7	61.3	
Stage 2	10.6 (44)		31.8	68.2	
Stage 3	34.6 (144)	51.84±33.75	29.2	70.8	0.002
Stage 4	29.3 (122)		18	82	
Stage 5	10.6 (44)		9.1	90.9	
Death	27.9 (116)		15.5	84.5	0.002
Comorbidity				80	
Hypertension	93.3 (388)		24.2	75.8	0.041
Diabetes	59.1 (246)		21.1	78.9	0.016
CAD	11.1 (46)		21.7	78.3	0.595
CCF	1 (4)		50	50	0.269
TIA	0.5 (2)		0	100	1.0
Renal Transplant patient	6.3 (26)		53.8	46.2	0.001
Renal stone	2.4 (10)		0	100	0.051
ADPKD	1.9 (8)		25	75	1.0
Hyperlipidaemia	48.6 (202)		26.7	73.3	0.576
Laboratory characteristic					
Serum Uric Acid µmol/L	17.3 (72)				
Normal	25.5 (106)				
Hyperuricemia	74.5 (301)				

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Total urine Protein 24h g/L				
< 0.15 g/L	56.7 (236)	33.1	66.9	
> 0.15 g/L	43.3 (180)	15.6	84.4	0.000
2x Serum Creatinine	39.9 (166)	22.9	77.1	0.192
Initiation of KRT	22.1 (92)	19.6	80.4	0.088

Table 1: *Demographic baseline characteristic data. eGFR (estimated glomerular filtration rate); CAD (coronary arteries diseases); CCF (congestive cardiac failure); PVD (Peripheral vascular disease); TIA (Transient ischemic attack); ADPKD (Autosomal Dominant Polycystic Kidney Disease); KRT (Kidney Replacement Therapy)*

PRIMARY OUTCOME

This study identified a significant association of hyperuricemia on several renal outcomes and mortality. The primary composite outcome of doubling of serum creatinine (39.9%), initiation of renal replacement therapy (22.1%), 50% GFR decline, and death (27.9%) from any cause was shown to occur in less than 40% (166 patients). A Kaplan Meier analysis was done to estimate the renal survival rate with hyperuricemia level. Doubling of serum creatinine and initiation of KRT was not shown to be associated with hyperuricemia level (Figure 1-4). However, high serum uric acid level was associated with a rapid GFR decline (50% eGFR decline, p = 0.057, Figure 3). Moreover, a significant association was also found between hyperuricemia level and all-cause mortality (n = 116, p = 0.005).

Kaplan Meier analysis

A Kaplan Meier analysis was performed to ascertain the effects of elevated serum uric acid level with renal outcome and mortality (Figure 1-4).

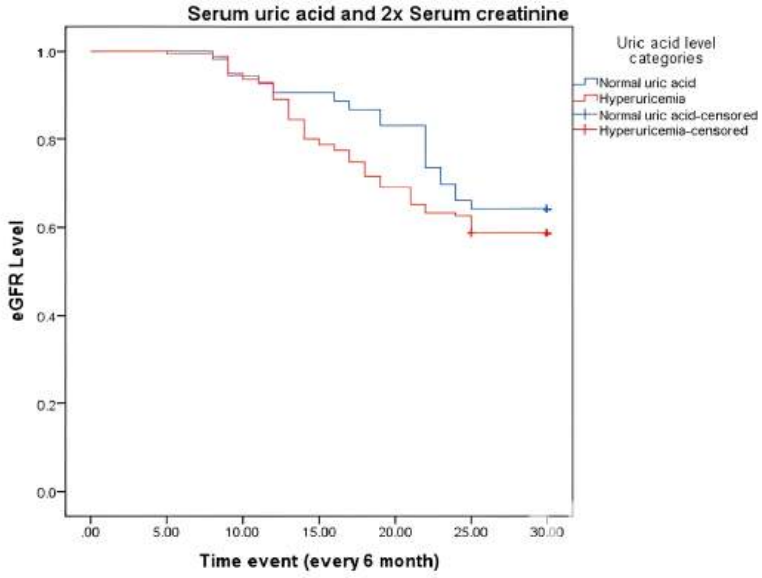

Figure 1: *A Kaplan Meier analysis was run to find the estimation of renal survival among those with high uric acid levels. Results showed that there were no significant differences in renal survival (doubling of serum creatinine) between those with normal uric acids vs hyperuricemia patients (p = 0.191)*

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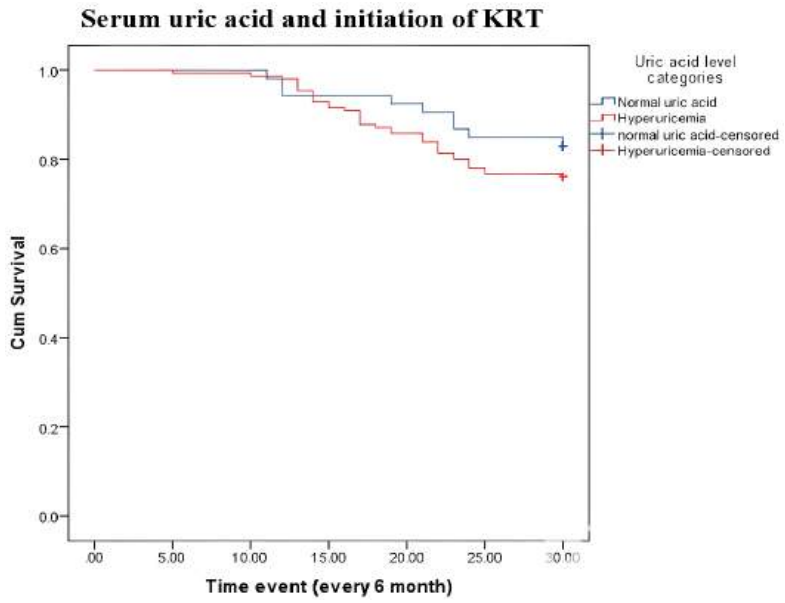

Figure 2: *A Kaplan Meier analysis was run to find the estimation of renal survival among those with high uric acid levels. Results showed that there were no significant differences in renal survival (initiation of KRT) between those with normal uric acids vs hyperuricemia patients (p = 0.136)*

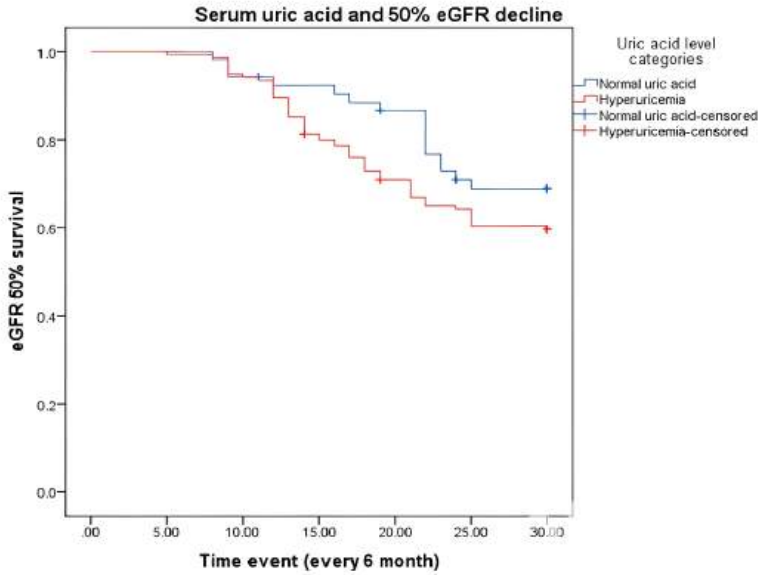

Figure 3: *A Kaplan Meier analysis was run to find the estimation of renal survival among those with high uric acid levels. Results showed that there was a significant difference in renal survival (50% eGFR decline) between those with normal uric acids vs hyperuricemia patients (p = 0.057)*

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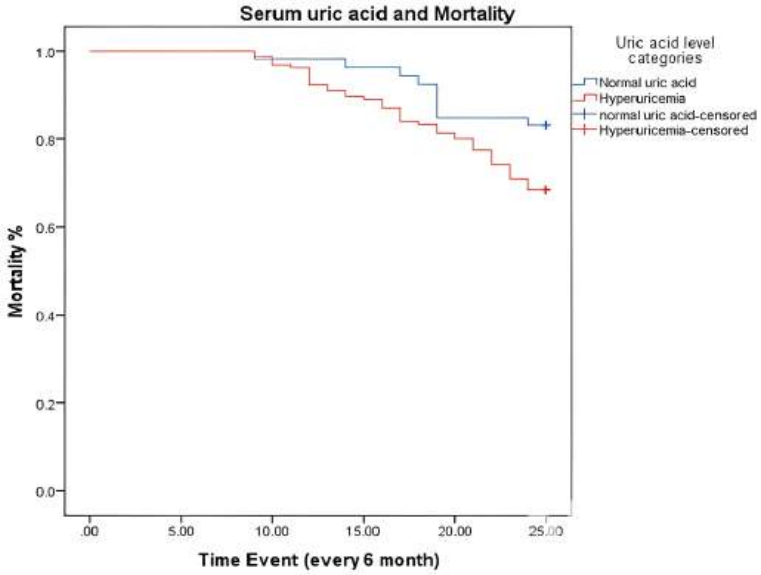

Figure 4: *A Kaplan Meier analysis was run to find the estimation of renal survival among those with high uric acid levels. Results showed that there was a significant difference in mortality between those with normal uric acids vs hyperuricemia patients (p = 0.005)*

SECONDARY OUTCOME

Furthermore, the other composite outcomes found a significant relationship between hyperuricemia with the renal outcome (total urinary protein, high level of serum creatinine, and reduction in eGFR level). Hyperuricemia has strong association with poorer secondary outcomes (proteinuria, serum creatinine and GFR level).

An increasing of serum uric acid level causing an elevated total urinary protein and serum creatinine (r=0.153 p=0.002, r = 0.182 p = 0.000*) and decreasing in GFR level (r = -0.237 p= 0.000*) [Figure 5-7].

Relationship of hyperuricemia with renal outcome

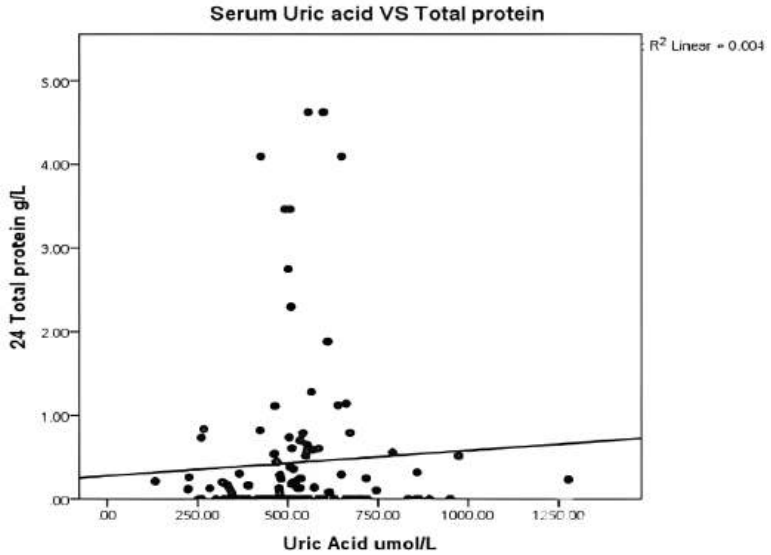

Figure 5: *Above diagram showed a correlation between serum uric acid with 24-hour total protein. Since the total protein is not normally distributed spearman correlation was chosen in this data analysis. There is a significant relationship of 24-hour total protein with serum uric acid (r = 0.153 p=0.002)*

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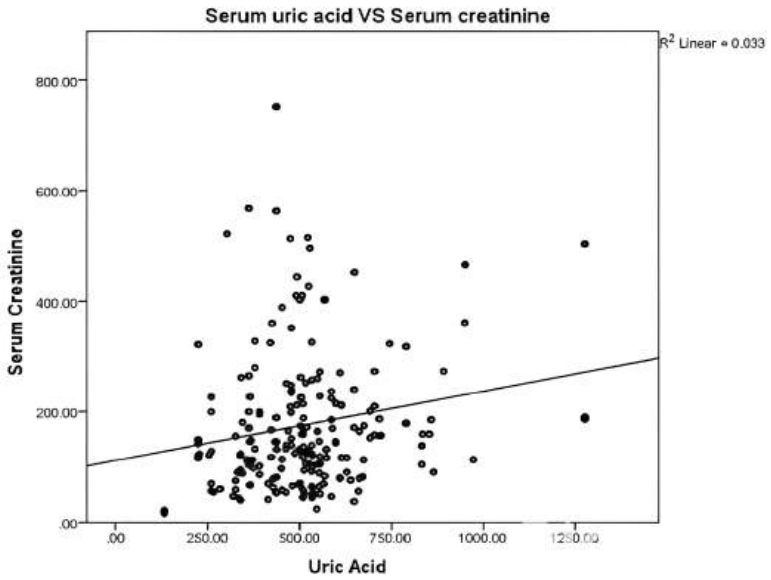

Figure 6: *A Pearson correlation was run to determine the relationship between serum uric acid and serum creatinine. There was a weak, positive correlation between serum uric acid and serum creatinine, which was statistically significant (r = 0.182, p = 0.000)*

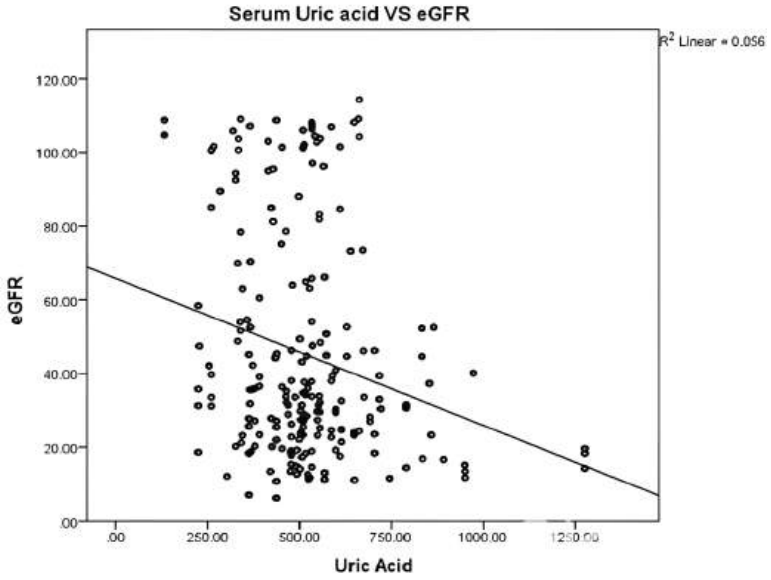

Figure 7: *A Pearson correlation was run to determine the relationship between serum uric acid and eGFR level. There was a weak, negative correlation between serum uric acid and eGFR level, which was statistically significant (r = -0.237, p = 0.000)*

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DISCUSSION

Studies as early as the 19th century has shown that uric acid is associated with various diseases and comorbidities, but never as an independent risk factor. This should be reconsidered as past studies have shown that the interstitial accumulation of sodium urate does induce progression in some diseases i.e. kidney and cardiovascular [14-15]. Uric acid has multiple biological actions, which included antioxidant effects on the neurologic system and a role in the immune system and pro-inflammatory pathways [16-20]. High concentration serum uric acid level is found to facilitate protein kinase, several cytokine and chemokine in causing proximal tubular dysfunction [21-23].

Based on our study, the baseline GFR tend to be lower in the presence of higher serum uric acid (Figure 7). Our study also has demonstrated a statistically significant association between high serum uric acid and poorer renal outcome. Additionally, survival analysis shows a statistically significant in 50 percent in GFR in the presence of hyperuricemia. On the other hand, the lack of renal survival benefit in term of doubling of serum creatinine (57% GFR reduction) and initiation of KRT with hyperuricemia could point towards a 'point of no return' effect of uric acid on kidney function whereby the tubulointerstitial inflammation and fibrosis induced by the urate acid could have been so severe that no meaningful recovery is possible by lowering the uric acid level subsequently.

There are several features of this study that make this conclusion robust. First, our result is consistent with Kamiya M el at., 2017 (Matched Cohort Study) [24], Momoki K et al., 2016 (Clinical Assessment of Prognostic Factor in Biopsy Proven Nephrosclerosis) [25] and Oh et al., 2019 (KNOW-CKD study) [15]. Our result does support the view that serum uric acid level is associated with rapid deterioration in renal function. Second, this study is the first study done in Malaysia with a larger sample size (n = 416). Third, this study provided more than 80% power in the number of populations to detect a clinically meaningful effect of high serum uric acid in rapid deterioration in renal decline with a longer duration of follow up more than 10 years. Fourth, this study included all CKD stages from Stage 1 up to Stage 5. The long duration of follow up of up to 13 years is another unique strength of this paper.

Data studying the clinical advantages of urate lowering therapy in CKD is notoriously and problematically heterogeneous. However, our study is different from CKD-FIX and PERL-CKD [26-28], in which those studies were designed to study the influence of serum uric acid lowering agent on the kidney function. First of all, both of the trials have a much shorter follow-up period (2 years in CKD-FIX and 3 years in PERL-CKD) as compared to ours.

Secondly, the CKD patients included in their study were in stage 3-4 while our study recruited patients from CKD stage 1-5. Additionally, the representation of Asian population is also low with only 5% patients in the CKD-FIX were Asians. PERL-CKD focuses more on the diabetic nephropathy population but not on the CKD population which give a non-broad-ranging assessment on the effect of serum uric acid level with kidney progression. Moreover, they also mentioned in their study, that their finding is inconsistent while comparing with other observational studies that have indicated that the serum uric acid level is a strong and independent predictor to renal decline. Interestingly, CKD-FIX has mentioned their result did not appear to support the view of high-level serum uric acid contributes to the worsening of CKD. Their findings reinforced our finding of hyperuricemia is associated with the 50 percent decline of GFR and an increase in mortality among CKD patients, yet high uric acid level have no effect on the more severe form of kidney function deterioration as mentioned earlier.

The exact role of uric acid influencing the progression of CKD is difficult and still being debated among researchers and clinicians. This is compounded by the fact that kidney is the main organ for uric acid excretion. A study by Johnson et al. demonstrated that that hyperuricemia could lead to systemic and glomerular hypertension via increased in renal vascular resistance and reduction in kidney perfusion. He has also shown that hyperuricemia could lead to oxidative stress and dysfunction in endothelial system. This invariably heighten the activity of the renin-angiotensin system (RAS) system resulting in glomerular and tubular fibrosis. Serum uric acid could also induce interstitial fibrosis through epithelial-to-mesenchymal transition which will lead to the fibrosis in CKD [29]. In this study, we put forward a possible a hypothesis that there is uric acid level threshold that could explain the heterogeneity of results of the previous trials on uric acid and CKD progression.

Our study does have some major limitations. First, this study is a single centre study. Second, this study did not list several medications (allopurinol or febuxostat, oral hypoglycaemic agent, ACE Inhibitor, antihypertensive and other related medication) and study their associations with renal progression. Other than that, this study used the Cockcroft and Gault formula (CG) equation for eGFR measurement, not CKD-EPI or MDRD that were used in other observational studies.

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CONCLUSION

In this Asian CKD cohort with a long duration of follow up, an increase in serum uric acid level is associated with rapid deterioration in renal function and mortality suggesting that it may play an independent predictor to rapid renal decline. We postulate there is a certain threshold point of uric acid induce irreversible kidney damage whereby further increment of uric acid level will not have any meaningful effect on kidney function. A further multicentre prospective study with a larger sample cohort is needed to address this research question.

CONFLICTS OF INTEREST

The authors declare that there are no potential conflicts of interest associated with this manuscript.

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