Madridge Journal of Diabetes

Research Article Open Access

Serum Uric Acid to Creatinine ratio as a marker of Estimated Glomerular Filtration Rate in type 2 diabetes patients

Sengsuk J[1], Tangvarasittichai O[2] and Tangvarasittichai S[2]*

[1]*Clinical Laboratory Unit, Ladyao Hospital, Nakhonsawan, Thailand*

[2]*Chronic Diseases Research Unit, Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand*

Article Info

***Corresponding author:**
Surapon Tangvarasittichai
Associate Professor
Chronic Diseases Research Unit
Department of Medical Technology
Faculty of Allied Health Sciences
Naresuan University
Phitsanulok, 65000
Thailand
Cell: +66055966276
Fax: +66-0-5596-6300
E-mail: surapon14t@yahoo.com

Received: April 3, 2018
Accepted: April 20, 2018
Published: April 26, 2018

Citation: Sengsuk J, Tangvarasittichai O and Tangvarasittichai S*. Serum Uric Acid to Creatinine ratio as a marker of Estimated Glomerular Filtration Rate in type 2 diabetes patients. *Madridge J Dia*. 2018; 2(1): 37-42.

Published by Madridge Publishers

Abstract

Chronic kidney disease (CKD) is a global health care problem; Serum creatinine (SCr), Serum uric acid (SUA) levels has shown to be the markers of renal disease progression. We aim to test renal function-normalized serum uric acid (SUA/SCr ratio and SUA*GFR/100; corresponding with their eGFR equation) as biomarkers of estimated glomerular filtration rate (eGFR) and CKD identification in type 2 diabetes mellitus (T2DM) patients. A total of 446 T2DM patients were included. Three eGFR equations were used as: Cockroft-Gault (eGFR1), the modification of diet in renal disease (MDRD) (eGFR2) and CKD-epidemiology collaboration (eGFR3) equation. Kruskal-Wallis test and Mann-Whitney *U*-test were used to compare the differences all groups and intergroup. ROC curve was used to indicate better marker, discrimination, and cut-off values generation. SUA*eGFR/100 and eGFR were significantly different in eGFR3 and caused the different values of SUA*eGFR/100 in total T2DM patients. The number of CKD patients (eGFR 30-59.9 ml/min/1.73 m^2) was different according to their eGFR equations and found significantly different in eGFR of each group and SCr, SUA, SUA/SCr ratio, and SUA*eGFR/100 in eGFR3 group. Bivariate correlation of SUA/SCr ratio, SUA*GFR/100 were significantly correlated with eGFR1, eGFR2, eGFR3 and the other variables both in total and in CKD group. SUA/SCr ratio, SUA*eGFR/100 with each eGFR equations cut-off values for CKD identification were generated.

Conclusion: SUA/SCr ratio can be used as a biomarker of GFR estimation and CKD identification, likely with eGFR but easier calculation. SUA/SCr ratio cut-off values were provided corresponding with their eGFR equations for selection.

Key words: Serum creatinine, Serum uric acid, estimated glomerular filtration rate, Cockroft-Gault, the modification of diet in renal disease, CKD-epidemiology collaboration.

Introduction

Kidney dysfunction and albuminuria are determinants as independent risk factors for chronic kidney disease (CKD) and cardiovascular disease (CVD) [1, 2]. Chronic kidney disease is a global health care problem; hyperglycemia and hypertension are the modifiable risk factors to control these factors are important for CKD prevention [3]. Patients with CKD may have one or more of these following, pathologic abnormalities, markers of kidney injury or damage (imaging, serum or urine sediment abnormalities and albuminuria), or GFR <60 mL per minute per 1.73 m^2 for at least three months [4]. Diabetes mellitus is the major and leading cause of CKD globally [5].

Serum creatinine (SCr), blood urea nitrogen (BUN) and serum uric acid (SUA) levels and urine analysis were commonly used for kidney function estimation [6]. However more evidences are demonstrated these biomarkers are not reach the optimal detection of the early stages of kidney disease [7-10]. The Kidney Disease Improving Global Outcomes recommends that glomerular filtration rate (GFR) is a determinant for diagnosis, classification and staging CKD [11]. GFR is the volume of body fluid filtered through the glomerular capillaries of the Bowman's capsule per unit time [12, 13]. GFR was usually used in clinical practice for drug dosing, diagnosis, prognosis and management in addition with public health and research works [14-16].

Serum creatinine (SCr) is a common marker for detecting the GFR changing and CKD stage, elevated SCr as a marker of renal disease and decreased renal function [17]. Similarly, elevated SUA level is also commonly observed in CKD patients. It is a simple biochemical marker for impaired or pathogenic role of kidney function [18, 19]. An elevated SUA was also associated with impaired renal function in type 2 diabetes mellitus (T2DM) patients [20], and used as predictor of development and progression of CKD in T2DM patients. [20, 21] In general physiological, renal clearance of SUA is often impaired during kidney injury or dysfunction, renal function is the major confounder in studies of the association between SUA with CKD progression [22].

The renal function-normalized SUA (SUA/SCr ratio and SUA*GFR/100) is studied before as the biomarker of the chronic obstructive pulmonary disease, metabolic syndrome and higher in the population with high prevalence of metabolic syndrome and T2DM [23, 24-26]. Because of the many formulas of the eGFR including sex, weight, race and many mathematic numbers were used in the clinical practice and provided the different results. But the SUA/SCr ratio is easier calculation by using the general biochemical markers no any additions. In the present study, we aim to demonstrate the renal function-normalized SUA (SUA/SCr ratio and SUA*GFR/100) [23] as the biomarkers for eGFR and CKD detection in T2DM patients.

Materials and Methods

Subjects

A total of 446 T2DM patients (overt diabetes more than 5 years) were randomized from the Diabetes Care Clinic of Ladyao Hospital during January 2015 to December 2016. All T2DM patients were receiving regular treatment with glycemic lowering, lipid lowering, and anti-hypertensive medication. The exclusion criteria were sustained heart failure, peripheral vascular disease, recent myocardial infarction, unstable angina, stroke, acute or chronic infection, cancer, hepatic disease, acute illness in the year of recruitment. All participants gave written informed consent. Our study protocol was approved by the Ethic committees of Naresuan University.

Physical and Biochemical Examination

All T2DM underwent anthropometry, blood pressure measurement and physical examination. Body mass index (BMI) was calculated and waist circumference (WC) was measured at the midpoint between the rib cage and the top of lateral border of iliac crest at minimum respiration. BP was measured after the participants had been seated and rested for 5 minutes, as the mean value of at least two measurements for these participants on the same day with calibrated desktop sphygmomanometers. Venous blood samples were collected from all participants without stasis after 8-12 hour fast in a seated position. Blood specimens were processed and assayed in the clinical laboratory of Ladyao Hospital, Nakhonsawan, Thailand. Plasma glucose (Glu), blood urea nitrogen (BUN), serum uric acid (SUA), total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C) were measured by enzymatic method. Serum creatinine (SCr) and urine creatinine (UCr) concentrations were determined based on the Jaffe reaction. Low density lipoprotein-cholesterol (LDL-C) concentrations were calculated with Friedewald's formula in specimens with TG levels <400 mg/dl. Urine samples were collected in polyethylene bottles after physical examination and blood taken for N-acetyl-β-D-glucosaminidase (NAG) and UCr determination. SUA/SCr ratio and SUA*GFR/100 were calculated according to their formula.

Hemoglobin A1C Measurement

HbA1c levels were assayed by using turbidimetric inhibition immunoassay (TINIA) on hemolyzed whole blood (standardized according to the International Federation of Clinical Chemistry) by use of a Hitachi 912 autoanalyzer (Roche Diagnostic, Switzerland)

High sensitivity-C-reactive protein (hs-CRP) Measurement

The hs-CRP levels were assayed by using latex-enhanced immunoneplelometric method on the Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) that has been standardized against the World Health Organization reference.

Urinary NAG (UNAG) Measurement

The assay is based on NAG in urine reacting with the substrate of p-nitrophenyl-N-acetyl- β -D-glucosaminide in sodium citrate buffer (pH 4.4) at 37 ºC to liberate p-nitrophenylate ion, then adding 2-amino-2-methyl-1-propanol (AMP) buffer (pH 10.25) to the reaction and measuring the color reaction with spectrophotometer at 405 nm [27] The within–run and between-run coefficient of variation in control material were 3.14% and 4.11% (n=10).

Estimated Glomerular Filtration Rate (eGFR)

The eGFR of each method was calculated by as follow:

The Cockroft-Gault Equation (eGFR1)

The Cockroft-Gault formula which incorporates age, body weight, and sex [28]. The formula is: eGFR1 = [(140 - age) * weight (kg) *constant]/[serum creatinine (μmol/L)] where 1.23 and 1.04 are constants for men and women, respectively.

The Modification of Diet in Renal Disease (MDRD) Equation (eGFR2)

The formula is: eGFR2 = 175 * (SCr) -1.154 * (age) -0.203 * 0.742 (If female) or 0.212 (If Black); SCr in mg/dl [29].

CKD-Epidemiology Collaboration Equation (eGFR3)

The formula is: eGFR3=141 * min (SCr/k, 1)$^{\alpha}$ * max (SCr/k, 1) $^{-1.209}$ * 0.993 $^{(age)}$ * 1.018 (If female) or 1.159 (If Black) [30]. Five eGFR stages according to clinical guidelines for chronic kidney disease of The Kidney disease outcome quality initiative advisory board were used: Stage I was normal eGFR (≥90ml/min/1.73 m^2); Stage II was mildly eGFR (60-89 mL/min/1.73 m^2); Stage III was moderately eGFR (30-59 ml/min/1.73 m^2); Stage IV was severely eGFR (<30 ml/min/ 1.73 m^2), and Stage V was end-stage renal disease: eGFR (<15 ml/min/1.73 m^2). An eGFR lower than 60 ml/min/1.73 m^2 (moderately eGFR) was defined as chronic kidney disease (CKD) [31].

Statistical Analysis

All data are presented as median and interquartile range for non-normally distributed data, tested by using Shapiro-Wilk test. All clinical characteristics, eGFR,SUA/SCr ratio, SUA*eGFR/100; corresponding with their eGFR equations were compared and CKD of these T2DM patients were identified (eGFR 30-59 ml/min/1.73 m^2) and compared clinical characteristics, number of patients according to each equation of eGFR calculation by using Kruskal-Wallis test, and compared the differences of intergroup by using Mann-Whitney *U*-test. Bivariate correlation between SUA/SCr ratio, SUA*eGFR/100, NAG, hs-CRP and with the other variables was assessed by using Spearman rank correlation test. A comparison of SUA/SCr ratio and SUA*eGFR/100 in CKD and non-CKD group of each eGFR equation were analyzed in terms of a receiver operating characteristic (ROC) curve. A ROC curve is a plot between sensitivity (Y-axis) versus false positive (X-axis), obtained for different cutoff points. Areas under the curve (AUC) of the ROC curves and their 95 per cent confidence intervals (CI) were evaluated as a measure of diagnostic accuracy. A discriminate analysis was performed to identify a combination of these parameters that provided the best differentiation between CKD and non-CKD individuals. Greater AUC of the ROC curve indicated better markers of the study. In general, an AUC of a ROC of 0.5 suggests no discrimination, whereas a maximal AUC of a ROC of 1 suggests outstanding discrimination and also generate the cut-off values of SUA/SCr ratio and SUA*eGFR/100 according to each equation of eGFR calculation [32]. All tests were two tailed, and *p*-values less than 0.05 were regarded as statistically significant. All analysis was performed by SPSS version 13.0 (SPSS, Chicago, IL, USA).

Results

The comparison of all clinical characteristics, SUA/SCr ratio, SUA*eGFR/100; corresponding with their eGFR equations of 446 T2DM patients by using the Kruskal-Wallis test and Mann-Whitney *U*-test were demonstrated in Table 1.

Table 1. Clinical characteristics and the comparison of eGFR and SUA*GFR/100 corresponding with their equation for eGFR calculation in type 2 diabetes mellitus patients by using Kruskal-Wallis test and Mann-Whitney *U*-test.

Variables	eGFR1 ml/min/1.73 m^2 (n=446)	eGFR2 ml/min/1.73 m^2 (n=446)	eGFR3 ml/min/1.73 m^2 (n=446)	*p*-value	*p*-Value eGFR1: eGFR2	*p*-Value eGFR1: eGFR3	*p*-Value eGFR2: eGFR3
Age (1Years)	54.0 (145.0-59.0)	54.0 (145.0-59.0)	54.0 (145.0-59.0)	-	-	-	-
BMI (1kg/m2)	22.8 (120.1-25.9)	22.8 (120.1-25.9)	22.8 (120.1-25.9)	-	-	-	-
WC (1cm)	82.5 (175.0-93.5)	82.5 (175.0-93.5)	82.5 (175.0-93.5)	-	-	-	-
Syst BP (1mmHg)	128.5 (1113.0-143.0)	128.5 (1113.0-143.0)	128.5 (1113.0-143.0)	-	-	-	-
Diast BP (1mmHg)	78.0 (169.0-85.0)	78.0 (169.0-85.0)	78.0 (169.0-85.0)	-	-	-	-
Glu (1mmol/l)	5.39 (14.79-6.82)	5.39 (14.79-6.82)	5.39 (14.79-6.82)	-	-	-	-
BUN (1mmol/l)	6.42 (14.28-20.33)	6.42 (14.28-20.33)	6.42 (14.28-20.33)	-	-	-	-
CT (1µmol/l)	113.15 (170.72-516.26)	113.15 (170.72-516.26)	113.15 (170.72-516.26)	-	-	-	-
SUA (1mmol/l)	380.67 (1297.40-481.79)	380.67 (1297.40-481.79)	380.67 (1297.40-481.79)	-	-	-	-
SUACT ratio	3.08 (11.04-4.57)	3.08 (11.04-4.57)	3.08 (11.04-4.57)	-	-	-	-
SUA*GFR/100	158.1 (152.0-261.3)	169.3 (146.1-260.4)	134.4 (120.4-251.5)	0.038	0.733	0.001	0.001
TC (1mmol/l)	4.63 (13.86-5.62)	4.63 (13.86-5.62)	4.63 (13.86-5.62)	-	-	-	-
TG (1mmol/l)	1.37 (11.02-2.08)	1.37 (11.02-2.08)	1.37 (11.02-2.08)	-	-	-	-
HDL-C (1mmol/l)	1.20 (10.93-1.55)	1.20 (10.93-1.55)	1.20 (10.93-1.55)	-	-	-	-
LDL-C (1mmol/l)	2.59 (11.96-3.28)	2.59 (11.96-3.28)	2.59 (11.96-3.28)	-	-	-	-
HbA1c	5.60 (15.10-6.58)	5.60 (15.10-6.58)	5.60 (15.10-6.58)	-	-	-	-
hs-CRP (1g/l)	5.87 (12.11-8.88)	5.87 (12.11-8.88)	5.87 (12.11-8.88)	-	-	-	-
NAG (1U/g CT)	28.82 (112.75-50.12)	28.82 (112.75-50.12)	28.82 (112.75-50.12)	-	-	-	-
eGFR (1ml/min/1.73 m2)	43.20 (111.50-83.38)	48.66 (19.25-85.41)	38.32 (13.91-82.73)	<0.001	0.705	0.001	0.002

SUA*eGFR/100 and eGFR are significantly different in eGFR3 Gr. These suggest that eGFR3 was significantly difference from the others and also caused the different values of SUA*eGFR/100 in total T2DM patients.

We found the difference number of subjects with eGFR 30-59.9 ml/min/1.73 m2 or CKD patients according to their eGFR equations. We also found significantly different in each eGFR group and significantly different in SCr, SUA, SUA/SCr ratio, and SUA*eGFR/100 in eGFR3 group as shown in Table 2.

Table 2. Comparison of the clinical characteristics of chronic kidney diseases group (eGFR3 30-59.9 ml/min/1.73 m ^{2}) by different equation for eGFR calculation in type 2 diabetes mellitus patients by using Kruskal-Wallis test and Mann-Whitney *U*-test.

Variables	eGFR1 30-59.9 ml/min/1.73 m^2 (1n=79)	eGFR2 30-59.9 ml/min/1.73 m^2 (1n=53)	eGFR3 30-59.9 ml/min/1.73 m^2 (1n=63)	*p*-value	*p*-Value eGFR1: eGFR2	*p*-Value eGFR1: eGFR3	*p*-Value eGFR2: eGFR3
Age (1Years)	65.0 (154.0-74.0)	58.0 (153.0-73.0)	63.0 (156.0-72.0)	0.354	0.259	0.857	0.158
BMI (1kg/m2)	23.3 (121.8-26.3)	23.5 (121.9-26.4)	24.5 (121.9-26.6)	0.592	0.810	0.311	0.508
WC (1cm)	86.0 (177.0-93.0)	85.0 (178.5-92.5)	87.0 (180.0-93.0)	0.888	0.771	0.842	0.614
Syst BP (1mmHg)	134.0 (1119.0-153.0)	133.0 (1114.5-152.5)	130.0 (1112.0-143.0)	0.593	0.666	0.313	0.584
Diast BP (1mmHg)	75.0 (168.0-87.0)	75.0 (168.5-80.0)	77.0 (169.0-89.0)	0.480	0.667	0.431	0.221
Glu (1mmol/l)	6.33 (15.39-7.98)	6.60 (15.47-8.47)	6.33 (15.34-8.20)	0.457	0.204	0.491	0.639
BUN (1mmol/l)	5.35 (13.92-8.56)	6.78 (14.28-8.38)	4.64 (13.92-6.78)	0.017	0.322	0.069	0.003
CT (1µmol/l)	97.24 (179.56-176.80)	114.92 (197.24-159.12)	97.24 (188.40-111.38)	<0.001	0.055	0.272	<0.001
SUA (1mmol/l)	380.67 (1309.29-469.89)	422.31 (1350.93-490.71)	380.67 (1297.40-416.36)	0.034	0.149	0.252	0.007
SUACT ratio	3.39 (12.78-4.44)	3.47 (12.79-4.13)	3.63 (13.29-4.53)	0.178	0.730	0.148	0.078
SUA*GFR/100	173.4 (1149.2-205.8)	193.2 (1162.4-220.9)	166.74 (1136.42-199.66)	0.038	0.098	0.392	0.020
TC (1mmol/l)	5.44 (14.54-5.91)	5.44 (14.70-6.09)	5.52 (14.88-6.37)	0.496	0.879	0.257	0.384
TG (1mmol/l)	1.53 (11.23-2.15)	1.64 (11.22-2.15)	1.53 (11.15-2.15)	0.957	0.992	0.793	0.800
HDL-C (1mmol/l)	1.30 (11.10-1.63)	1.29 (10.99-1.68)	1.34 (11.14-1.74)	0.553	0.825	0.369	0.332
LDL-C (1mmol/l)	3.08 (12.45-3.73)	2.89 (12.30-3.61)	3.10 (12.55-3.67)	0.436	0.597	0.432	0.192
HbA1c	5.86 (15.20-6.93)	5.70 (15.20-6.60)	5.60 (15.25-6.60)	0.879	0.631	0.793	0.946
hs-CRP (1g/l)	6.64 (14.18-9.13)	7.21 (16.05-11.16)	7.87 (16.21-11.99)	0.021	0.295	0.548	0.748
NAG (1U/g CT)	38.37 (124.45-56.48)	37.70 (127.99-63.91)	39.46 (128.41-65.96)	0.051	0.506	0.448	0.684
eGFR (1ml/min/1.73 m^2)	41.39 (136.55-54.72)	45.98 (136.84-53.49)	47.31 (139.26-54.41)	<0.001	<0.001	<0.001	0.020

Bivariate correlation, SUA/SCr ratio was significantly correlated with the other variables and significantly correlated with eGFR1, eGFR2, eGFR3 both in total patients and CKD patients (eGFR 30-59.9 ml/min/1.73 m2) as shown in Table 3.

Table 3. Bivariate correlation of these variables in type 2 diabetes patients.

Correlation between parameters		Correlation coefficient r	p-value	Correlation between parameters		Correlation coefficient r	p-value
SUA/SCr	Glu	-0.190	<0.001	TG	Age	0.325	<0.001
	BUN	-0.802	<0.001		Syst BP	0.234	<0.001
	TC	0.389	<0.001		Diast BP	0.124	0.009
	HDL-C	0.510	<0.001		WC	0.241	<0.001
	LDL-C	0.400	<0.001		BMI	0.205	<0.001
	HbA1c	-0.116	0.048		BUN	0.177	<0.001
	hs-CRP	-0.620	<0.001		HDL-C	-0.363	<0.001
	NAG	-0.619	<0.001		LDL-C	0.115	0.015
	WC	-0.246	<0.001		HbA1c	0.245	<0.001
	Syst BP	-0.254	<0.001		NAG	0.197	0.001
SUA	Glu	0.211	<0.001		Hs-CRP	0.332	<0.001
	BUN	0.638	<0.001	TC	Age	0.218	<0.001
	TC	-0.205	<0.001		BUN	-0.372	<0.001
	TG	0.302	<0.001		TG	0.291	<0.001
	HDL-C	-0.407	<0.001		HDL-C	0.451	<0.001
	LDL-C	-0.243	<0.001		Hs-CRP	-0.199	0.001
	HbA1c	0.225	<0.001		NAG	-0.205	<0.001
	Hs-CRP	0.485	<0.001		WC	-0.106	0.025
	NAG	0.353	<0.001	HDL-C	BUN	-0.522	<0.001
	WC	0.220	<0.001		HbA1c	-0.184	0.002
	Syst BP	0.250	<0.001		Hs-CRP	-0.431	<0.001
SCr	Glu	0.246	<0.001		NAG	-0.327	<0.001
	BUN	0.866	<0.001		WC	-0.231	<0.001
	SUA	0.639	<0.001		Syst BP	-0.142	0.003
	TC	-0.389	<0.001		Age	-0.198	<0.001
	TG	0.178	<0.001		BUN	-0.856	<0.001
	HDL-C	-0.562	<0.001		LDL-C	0.392	<0.001
	LDL-C	-0.406	<0.001		HbA1c	-0.149	0.011
	HbA1c	0.132	0.024		Hs-CRP	-0.610	<0.001
	Hs-CRP	0.617	<0.001		NAG	-0.613	<0.001
	NAG	0.625	<0.001		WC	-0.271	<0.001
	WC	0.298	<0.001		BMI	0.103	0.030
	Syst BP	0.328	<0.001		Syst BP	-0.343	<0.001
Glu	Age	0.425	<0.001				
	BUN	0.226	<0.001				
	SCr	0.246	<0.001				
	TC	0.124	0.009				
	TG	0.313	<0.001				
	HDL-C	-0.121	0.011				
	HbA1c	0.382	<0.001				
	Hs-CRP	0.414	<0.001				
	NAG	0.397	<0.001				
	WC	0.330	<0.001				
	BMI	0.200	<0.001				
	Syst BP	0.246	<0.001				

We plotted the ROC curves for SUA/SCr ratio and SUA*eGFR/100; corresponding with their eGFR equations. The results of SUA/SCr ratio and SUA*eGFR/100; corresponding with their eGFR equations ROC curve analysis showed that each marker is a significant discriminator for eGFR in CKD patients. The area under the curve (AUC) of the ROC curve was used for prediction of better markers for each eGFR in CKD patients. The AUC results were obtained with 0.877 of SUA/SCr ratio and 0.928 of SUA*eGFR1/100 (Fig 1A), 0.944 of SUA/SCr ratio and 0.958 of SUA*eGFR2/100 (Fig 1B), and 0.928 of SUA/SCr ratio and 0.974 of SUA*eGFR3/100 (Fig 1C), indicating that these models with these ratios can be used for estimating the glomerular filtration rate of T2DM patients in this study (Table 4, Fig 1).

Table 4. Bivariate correlation of GFR1, GFR2, GFR3, SUA:SCr ratio, and SUA*GFR*100 corresponding with their eGFR equations in total, CKD and all eGFR<60 mi/min/1.73 m^2 groups of type 2 diabetes patients.

Correlation of	Total (n=446)	eGFR 30-59.9 ml/min/1.73 m ^{2} (n= in each group)	eGFR<60.0 ml/min/1.73 m ^{2} (n= in each group)
eGFR1 with SUA:SCr ratio	r=0.881; p<0.001	r=0.343; p=0.002	r=0.902; p<0.001
eGFR2 with SUA:SCr ratio	r=0.904; p<0.001	r=0.570; p<0.001	r=0.0.933; p<0.001
eGFR3 with SUA:SCr ratio	r=0.906; p<0.001	r=0.628; p<0.001	r=0.896; p<0.001
eGFR1 with SUA*GFR1*100	r=0.931; p<0.001	r=0.306; p<0.001	r=0.933; p<0.001
eGFR2 with SUA*GFR2*100	r=0.930; p<0.001	r=0.538; p<0.001	r=0.947; p<0.001
eGFR3 with SUA*GFR3*100	r=0.963; p<0.001	r=0.797; p<0.001	r=0.950; p<0.001
eGFR1 with eGFR2	r=0.973; p<0.001	r=0.701; p<0.001	r=0.682; p<0.001
eGFR1 with eGFR3	r=0.968; p<0.001	r=0.651; p<0.001	r=0.619; p<0.001
eGFR2 with eGFR3	r=0.984; p<0.001	r=0.904; p<0.001	r=0.857; p<0.001
SUA*GFR1/100 with SUA* GFR2/100	r=0.966; p<0.001	r=0.745; p<0.001	r=0.745; p<0.001
SUA*GFR1/100 with SUA* GFR3/100	r=0.950; p<0.001	r=0.510; p<0.001	r=0.510; p<0.001
SUA*GFR2/100 with SUA* GFR3/100	r=0.971; p<0.001	r=0.797; p<0.001	r=0.797; p<0.001

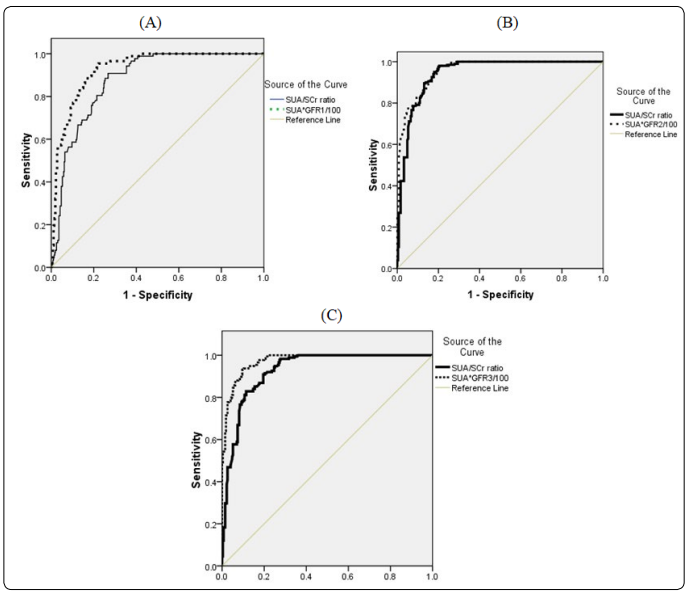

Figure 1. The ROC curve of SUA/SCr ratio and SUA*GFR/100 corresponding with their eGFR equations [eGFR1 (A), eGFR2 (B) and eGFR3 (C)] in the present study.

The optimal cut-off values of SUA/SCr ratio, SUA*eGFR/100; corresponding with their eGFR equations, for prediction of CKD in present study were 3.60 with sensitivity and specificity of 90.8%, and 73.0%; 220 with sensitivity and specificity of 90.8% and 79.9%, corresponding with their eGFR1 equations, 3.19 with sensitivity and specificity of 89.6%, and 86.9%; 175.0 with sensitivity and specificity of 85.1.8% and 93.9%, corresponding with their eGFR2 equations, and 3.18 with sensitivity and specificity of 90.9%, and 80.4%; 175 with sensitivity and specificity of 91.4% and 90.4%, corresponding with their eGFR3 equations, respectively (Table 5).

Table 5. The AUC of SUA/CT ratio and SUA*GFR/100 corresponding with their eGFR equations in the present study.

Area Under the Curve									
Test Result Variable(s)	Area	Std. Error	Asymptotic 95% Confidence Interval		p-value	Cut-off value	Specificity (%)	Sensitivity (%)	
			Lower Bound	Upper Bound					
SUA/SCr ratio	0.877	0.017	0.844	0.910	<0.001	3.60	90.8	73.0	Fig 1 (A)
SUA*GFR1/100	0.928	0.013	0.904	0.953	<0.001	220	90.8	79.9	
SUA/SCr ratio	0.944	0.010	0.924	0.965	<0.001	3.19	89.6	86.9	Fig 1 (B)
SUA*GFR2/100	0.958	0.008	0.942	0.973	<0.001	175.0	85.1	93.9	
SUA/SCr ratio	0.928	0.012	0.905	0.951	<0.001	3.18	90.9	80.4	Fig 1 (C)
SUA*GFR3/100	0.974	0.006	0.962	0.985	<0.001	175.0	91.4	90.4	

The different number of individual having lower cut-off value of SUA/SCr ratio and eGFR<60.0 ml/min/1.73 m^2 (CKD) were identified by using their SUA/SCr ratio values and their eGFR equation as shown in the Table 6.

Table 6. Total number of individual having CKD or eGFR<60 mi/min/1.73 m^2 groups and SUA/SCr ratio cut-off value corresponding with their eGFR equations.

eGFR equation	Number of eGFR <60ml/min/1.73 m^2	SUA (mmol/l)	SCr(μmol/l)	SUA/SCr ratio	UA*GFR/100
eGFR1	267	452.05 (1362.83-553.16)	395.15 (1177.68-736.37)	1.26 (10.58-2.78)	70.53 (133.04-142.50)
eGFR2	245	463.94 (1395.54-573.98)	434.93 (1205.97-756.70)	1.16 (10.54-2.30)	59.99 (131.79-125.65)
eGFR3	271	452.05 (1374.72-553.16)	380.12 (1177.68-731.07)	1.28 (10.59-2.86)	71.59 (133.10-153.07
SUA/SCr<3.60	269	440.15 (1315.24-547.22)	380.12 (1177.68-733.72)	1.27 (10.58-2.62)	71.59 (133.07-142.53)
SUA/SCr<3.19	234	457.99 (1349.45-566.55)	468.96 (1229.18-766.87)	1.11 (10.53-2.04)	49.73 (121.93-105.64)
SUA/SCr<3.18	233	457.99 (1347.96-562.09)	469.40 (1229.84-767.31)	1.10 (10.53-2.02)	22.04 (18.16-64.70)

Discussion

Estimating GFR was very important and usually used in clinical practice for drug dosing, diagnosis, prognosis and management in addition with public health and renal research works [14-16]. The most commonly used equations including Cockroft-Gault (eGFR1) [28], MDRD (eGFR2) [29, 33], CKD-EPI (eGFR3) [30] and more equations that combines creatinine and CysC [34]. The results of CKD-EPI were significantly lower estimated CKD than the MDRD equation [33]. While the MDRD equation underestimates GFR in healthy individuals resulting in false negative diagnosis of CKD in this population [35].

The present study demonstrated that MDRD equation (eGFR2) resulted in higher eGFR and gave lower in number of CKD patients, and CKD-EPI equation (eGFR3) resulted in lower eGFR and gave higher in number of CKD patients, while Cockroft-Gault equation (eGFR1) resulted in the middle of these 2 equations. Our results demonstrated the same cut-off values (<3.19 and <3.18) of SUA/SCr ratio according to eGFR2 and eGFR3 and also identified the same number of CKD patients, while the SUA/SCr ratio cut-off value = <3.60 according to eGFR1 and also identified the higher number of CKD patients.

Only SUA has been shown a predictor for the progression of renal disease caused from the association of SUA and eGFR, but not all studies [36, 37].In impaired renal function, increasing of SUA was occurred as a consequence of CKD as a strong predictor for renal disease progression. Patients with lower eGFR were higher in SUA levels and higher risks in progression of renal disease. Then, baseline renal function-normalized SUA (SUA/SCr ratio, SUA*eGFR/100), which may reflect the net production of SUA, will be better than only SUA value as the predictor of incident CKD. The Modification of Diet in Renal Disease (MDRD) Study also failed to demonstrate SUA as the predictor for progression of chronic renal failure after a 10-year follow-up in 840 individuals with CKD [20, 38, 39]. SUA/SCr ratio is studied before as the biomarker of the chronic obstructive pulmonary disease, metabolic syndrome and higher in the population with high prevalence of metabolic syndrome and T2DM [24-27].

Conclusion

The present study demonstrated SUA/SCr ratio and SUA*eGFR/100 was significantly correlated with each eGFR equations.SUA/SCr ratio can be used as a biomarker of GFR estimation in the same as eGFR but easier calculation by using the general biochemical markers no any additions. We also provide the SUA/SCr ratio cut-off value according to eGFR equations for selection.

Acknowledgement

We sincerely thank Ladyao Hospital and all co-workers of Clinical Laboratory, Ladyao Hospital for their technical assistance and supporting. We sincerely thank Asst. Prof. Dr. Ronald A. Markwardt, Burapha University, for his reading and correcting of the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet.* 2010; 375(9731): 2073-2081. doi: 10.1016/S0140-6736(10)60674-5
2. Nagata M, Ninomiya T, Kiyohara Y, Murakami Y, Irie F, Sairenchi T, et al. Prediction of cardiovascular disease mortality by proteinuria and reduced kidney function: Pooled analysis of 39,000 individuals from 7 cohort studies in Japan. *Am J Epidemiol.* 2013; 178(1): 1-11. doi: 10.1093/aje/kws447
3. Carney EF. Epidemiology: Global Burden of Disease Study 2013 reports that disability caused by CKD is increasing worldwide. *Nat Rev Nephrol.* 2015; 11: 446. doi: 10.1038/nrneph.2015.98
4. Baumgarten M, Gehr T. Chronic Kidney Disease: Detection and Evaluation. *Am Fam* Physician. 2011; 84(10): 1138-1148.
5. Ritz E, Rychlik I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. *Am J Kidney Dis.* 1999; 34(5): 795-808. doi: 10.1016/S0272-6386(99)70035-1
6. Rehberg PB. Studies on Kidney Function: The Rate of filtration and reabsorption in the human kidney. *Biochem J.* 1926; 20(3): 447-460.
7. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S. Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. *Am J Med.* 1983; 75(6): 943-950. doi: 10.1016/0002-9343(83)90873-2
8. Waikar SS, Betensky RA, Bonventre JV. Creatinine as the gold standard for kidney injury biomarker studies? *Nephrol Dial Transplant.* 2009; 24(11): 3263-3265. doi: 10.1093/ndt/gfp428
9. Bjornsson TD. Use of serum creatinine concentrations to determine renal function. *Clin Pharmacokinet.* 1979; 4(3): 200-222.
10. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. *Intensive Care Med.* 2004; 30(1): 33-37. doi: 10.1007/s00134-003-2078-3
11. Gaspari F, Perico N, Remuzzi G. Application of newer clearance techniques for the determination of glomerular filtration rate. *Curr Opin Nephrol Hypertens.*1998; 7(6): 675-680.
12. Mccance RA, Robinson JR. Evaluation of renal clearances. *Proc R Soc Med.* 1949; 42(7): 475-480.
13. Smith HW, Goldring W, Chasis H. The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. *J Clin Invest.* 1938; 17(3): 263-278. doi: 10.1172/JCI100950
14. Soares AA, Eyff TF, Campani RB, Ritter L, Camargo JL, Silveiro SP. Glomerular filtration rate measurement and prediction equations. *Clin Chem Lab Med.* 2009; 47(9): 1023-1032. doi: 10.1515/CCLM.2009.263
15. Ruggenenti P, Gaspari F, Cannata A, Carrara F, Cella C, Ferrari S, et al. Measuring and estimating GFR and treatment effect in ADPKD patients: results and implications of a longitudinal cohort study. *Plos One.* 2012; 7. doi: 10.1371/journal.pone.0032533
16. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis.* 2014; 63(5): 820-834. doi: 10.1053/j.ajkd.2013.12.006
17. Dalton RN. Serum creatinine and glomerular filtration rate: perception and reality. *Clin Chem.* 2010; 56(5): 687-689. doi: 10.1373/clinchem.2010.144261
18. Odden MC, Amadu AR, Smit E, Lo L, Peralta CA. Uric acid levels, kidney function, and cardiovascular mortality in US adults: National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 1999-2002. *Am J Kidney Dis.* 2014; 64(4): 550-557. doi: 10.1053/j.ajkd.2014.04.024
19. Nashar K, Fried LF. Hyperuricemia and the progression of chronic kidney disease: is uric acid a marker or an independent risk factor? *Adv Chronic Kidney Dis.* 2012; 19(6): 386-391. doi: 10.1053/j.ackd.2012.05.004
20. Zoppini G, Targher G, Chonchol M, Ortalda V, Abaterusso C, Pichiri I, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. *Diabetes Care.* 2012; 35(1): 99-104. doi: 10.2337/dc11-1346
21. Kim WJ, Kim SS, Bae MJ, Yi YS, Jeon YK, Kim BH, et al. High-normal serum uric acid predicts the development of chronic kidney disease in patients with type 2 diabetes mellitus and preserved kidney function. *J Diabetes Complications.* 2014; 28(2): 130-134. doi: 10.1016/j.jdiacomp.2013.11.006
22. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension.* 2003; 41(6): 1183-1190. doi: 10.1161/01.HYP.0000069700.62727.C5
23. Gu L, Huang L, Wu H, Lou Q, Bian R. Serum uric acid to creatinine ratio: A predictor of incident chronic kidney disease in type 2 diabetes mellitus patients with preserved kidney function. *Diab Vasc Dis Res.* 2017; 14(3): 221-225. doi: 10.1177/1479164116680318
24. Garcia-Pachon E, Padilla-Navas I, Shum C. Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease. *Lung.* 2007; 185(1): 21-24. doi: 10.1007/s00408-006-0076-2
25. Kocak ND, Sasak G, Aka Akturk U, Akgun M, Boga S, Sengul A, et al. Serum Uric Acid Levels and Uric Acid/Creatinine Ratios in Stable Chronic Obstructive Pulmonary Disease (COPD) Patients: Are These Parameters Efficient Predictors of Patients at Risk for Exacerbation and/or Severity of Disease? *Med Sci Monit.* 2016; 22: 4169-4176. doi: 10.12659/MSM.897759
26. Aljohani NJ. Metabolic syndrome: Risk factors among adults in Kingdom of Saudi Arabia. *J Family Community Med.* 2014; 21(3): 170-175. doi: 10.4103/2230-8229.142971
27. Horak E, Hopfer SM, Sunderman FW Jr. Spectrophotometric assay for urinary N-acetyl-β-D glucosaminidase activity. *Clin Chem.* 1981; 27(7): 1180-1185.
28. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16(1): 31-41. doi: 10.1159/000180580
29. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999; 130(6): 461-470. doi: 10.7326/**:** 0003-4819-130-6-199903160-00002
30. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009; 150(9): 604-612. doi: 10.7326/0003-4819-150-9-200905050-00006
31. National Kidney Foundation. Kidney disease outcome quality initiative advisory board. Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39(2 Suppl 1): S1-246.
32. Swets JA. Measuring the accuracy of diagnostic systems. *Science.* 1988; 240(4857): 1285-1293. doi: 10.1126/science.3287615
33. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem.* 2007; 53(4): 766-772. doi: 10.1373/clinchem.2006.077180
34. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012; 367: 20-29. doi: 10.1056/NEJMoa1114248
35. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med.* 2004; 141(12): 929-937. doi: 10.7326/0003-4819-141-12-200412210-00009
36. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F, MMKD Study Group. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. *Exp Gerontol.* 2008; 43(4): 347-352. doi: 10.1016/j.exger.2008.01.006
37. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes care.* 2009; 32(9): 1737-1742. doi:10.2337/dc09-0288
38. Ohta Y, Tsuchihashi T, Kiyohara K, Oniki H. Increased uric acid promotes decline of the renal function in hypertensive patients: a 10-year observational study. *Intern Med.* 2013; 52(13): 1467-1472. doi: 10.2169/internalmedicine.52.0141
39. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, et al. Uric acid and long-term outcomes in CKD. *Am J Kidney Dis.* 2009; 53(5): 796-803. doi: 10.1053/j.ajkd.2008.12.021