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Evaluation of Uric Acid and Its Correlation with Decline in Estimated Glomerular Filtration Rate among the Chronic Kidney Disease Patients

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Abstract: Chronic kidney disease is one of the most serious public health burdens globally, with significant morbidity, mortality, and compromise patient life expectancy. Many sub-Saharan African countries face double-burden challenges in the treating of chronic kidney disease and its associated complications. The current study aims to evaluate serum uric acid, and its correlation with estimated glomerular filtration rate as well as other risk factors among the chronic kidney disease patients on follow-up at renal clinic of Jimma University specialized referral hospital. An Institution-based cross-sectional study was conducted at Jimma University referral from August 6, 2022, to November 13, 2022. A consecutive sampling technique was employed to recruit the study participants into the current study. Data were collected using interviewer-based structured questionnaires and patient's record reviews. The collected data were analyzed by SPSS version 25.0. Pearson's correlation analyses was used to check the correlation between estimated glomerular filtration rate and uric acid. Univariate and multivariate linear regression model was used to test predictors of serum uric acid in the study participants. The total study participants were 140 individuals. Subjects included (54.3% [n=76]) men and (45.7% [n=64]) women, respectively. The mean (SD) age of study subjects was 51.04±9.02 years. The mean value of serum uric acid was 7.2±2.1mg/dl whereas the mean of estimated glomerular filtration rate (eGFR) was 54.2±31 mL/min/1.73m^2. Furthermore, the mean values of serum creatinine and blood urea nitrogen among participants in this study were 3.2±1.4 and 67.8±35.8 mg/dL respectively. In the current study, estimated glomerular filtration rate (eGFR) value was negatively correlated (r=-0.912, P<0.001) with uric acid. However, systolic blood pressure was positively correlated (r=0.584, P<0.001) with uric acid. Moreover, the eGFR value was negatively associated (β=-0.060, P=<0.001) with uric acid among study participants. Based on the current study finding, an increase in serum uric acid was associated with a decrease in eGFR value. Increased serum uric acid, increased body mass index and high blood pressure are independent risk factors for disease progression in patients with CKD.

Keywords: Serum Uric Acid, Chronic Kidney Disease, Body Mass Index, Estimated Glomerular Filtration Rate

1. Introduction

Chronic kidney disease is associated with significant morbidity and mortality in both developed and developing nations [1]. Even though the disease affects worldwide population, 78% of chronic kidney disease patients reside in low and middle-income countries [2]. Many sub-Saharan African countries, including Ethiopia face double-burden challenges in treating chronic kidney disease and its complications [3]. The prevalence of the disease has increased rapidly in Africa, with 11% in Tunisia, 17.3% Ethiopia and 83.7% in Tanzania, respectively [4].

Diabetic kidney disease (DKD) explained by eGFR

<60ml/min/m^2 and micro/macroalbuminuria is the most common small vasculature complication of diabetes mellitus that leads to ESRD [5]. High blood pressure is another disease associated with chronic kidney disease whose prevalence ranges from 60% to 90% depending on the stage and cause of CKD [6]. Studies in the USA show hypertension as a leading cause of end-stage renal disease and associated with a high risk of cardiovascular morbidity and mortality [7].

There are also several risk factors associated with CKD susceptibility and fasten the diseases to end-stage renal disease (ESRD). Heavy alcohol consumption is associated with high-risk factors for CKD and progression to end stage renal disease [8]. Kidney damage from alcohol consumption is mainly due to its byproducts (acetaldehydes, and free radicals) generated during alcohol metabolism [9]. Similarly, cigarette smoking is associated with cardiovascular disease, liver disease, and decreased kidney function [10]. The possible mechanism is that nicotine in cigarettes induces free radicals' production which can damage kidney cells [11].

The causes of the inflammatory process in CKD include overproduction of inflammatory cytokines, uremic toxins, diminished defense mechanism, and metabolic acidosis [12, 13]. Hyperuricemia is a condition characterized by abnormal elevation of serum uric acid above normal level (normal SUA level <6.8mg/dl). There are several potential mechanisms through which hyperuricemia can fasten the progression of chronic kidney disease. The precipitation of urate in renal tubules can cause renal nephropathy through the formation of crystals that induces the release of various proinflammatory cytokines to cause chronic interstitial inflammation and fibrosis. [14]. Hyperuricemia may also induce proliferation of vascular smooth muscle cells, expression of cyclo-oxygenase-2 enzyme (COX-2), and renal renin, leading to arteriopathy and hypertension which further aggravate reduction of kidney function [15-17]. Hyperuricemia is an independent risk factor for the decline in renal function, and the incidence of hyperuricemia increases with the decrease of estimated glomerular filtration rate [18]. Studies showed that more than 90% of hyperuricemia is caused by the inefficient capacity of renal to clear uric acid [19].

Study conducted in China found a nonlinear positive relationship between serum uric acid and eGFR [20]. Another study proposed that serum levels of urate increase linearly with decreasing eGFR as result of decreased uric acid excretion. However, this finding didn't discriminate whether the elevated serum uric acid play a causative role in the progression of CKD or indirect markers of disease progression [21]. A study conducted in Thailand revealed that there was an independent association between serum uric acid levels with the incidence of impaired renal function and renal progression in the CKD population [22].

Study in Korea found that a high uric acid level should be considered as a factor that is potentially related to kidney dysfunction [23]. Study conducted in Netherland among 2601 subjects suggest that hyperuricemia is independently associated with a decline in renal function [24]. The possible mechanism was explained by recent studies suggest mechanisms of damage of hyperuricemia other than the traditional precipitation of urate into the tubules. In animal models, hyperuricemia induces the development of a glomerular arteriolopathy that impairs renal autoregulation and causes glomerular hypertension, leading eventually to glomerulosclerosis and interstitial fibrosis. Both factors are well-known related to the progression of kidney disease [25].

It is known that glomerular filtration rate (GFR) has been used for early screening, diagnosis and monitoring of kidney function [26]. However, eGFR is measured by clearance techniques that use substances such as creatinine as markers of filtration [27]. Serum creatinine is responsible for the variability and decrease in the sensitivity of eGFR to detect chronic kidney disease [28]. Additionally, in most case chronic kidney diseases do not show symptoms or findings until the disease become advanced and associated with complications [29]. Therefore, early detection of renal impairment and following disease progression is crucial to require measures that minimize adverse outcomes [30]. Consequently, searching for parameters that correlate with eGFR contribute is an additional option for early screening and monitoring of the disease that results in reducing hospitalization, complication, early death from the disease. Therefore, a recent study aimed to evaluate serum uric acid and its correlation with decline in eGFR in chronic kidney disease patients.

2. Methods and Materials

2.1. Study Setting and Design

The study was conducted at Jimma University referral hospital from August 6, 2022, to November 13, 2022. The study design was hospital based cross-sectional study design. Jimma University referral hospital. The hospital is located in southwestern Ethiopia and far 356 Km from the capital city of the Ethiopia (Addis Ababa).

2.2. Study Participants and Sample Size

The source population was the already known chronic kidney disease and on follow-up at renal clinic of the Jimma University referral hospital. All CKD patients who had visited Jimma University referral hospital during the study and were willing to participate in the study included in the study. As exclusion criteria, chronic kidney patients with acute and chronic liver disease, malignant disease, dialysis patients, patients with musculoskeletal deformities, and critically ill patients who were unable to cooperate were excluded from the study.

The sample size was determined by a single population proportion formula, prevalence of hyperuricemia in patients with renal disease (p=15.2), 95% CI, 5% precision, considering a 10% non-response rate. Finally, one hundred forty (140) chronic kidney disease on follow-up were recruited using consecutive sampling techniques.

2.3. Data Collections and Measurement Procedure

Data including sociodemographic factors, behavior, and

medical histories of eligible participants was collected by interviewer-administered structured questionnaires. Records of height, weight, and blood pressure were done at immediate contact of patients.

Body mass index (BMI) was calculated using weight and height computed as weight in kilograms divided for height in meter. BMI is classified as follows: BMI ≤ 18.5 Kg/m^2 underweight, BMI = 18.5-24.9 Kg/m^2 normal weight, BMI = 25-29.9 Kg/m^2 overweight and BMI ≥ 30 Kg/m^2 obese [31].

Blood pressure was measured using the Omron digital BP measuring device (HEM907, Kyoto, Japan) on the right upper arm after participants had been seated and resting quietly for at least five minutes. Therefore, if systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg are considered hypertension, respectively [32].

2.4. Laboratory Measurements

Blood sample was drawn from eligible participants to determine serum creatinine, blood urea nitrogen, and uric acid level. The sample was measured in a single laboratory using an automated clinical chemistry analyzer (Coobas400; Horiba France, Longjumeau Cedex, France). Internal quality was ensured by running control test every day before analyzing patients' sera.

2.5. Serum Uric Acid Measurement

Principle of the method: Serum uric acid was measured by the uricase method. Uric acid is oxidized to allantoin and hydrogen peroxide (H_2O_2) by the uricase enzyme. Phenolic compound and 4-amino-antipyrines react with hydrogen peroxide to form red-colored quinonimine dye complex by the catalytic action of the peroxidase enzyme. The absorbance of light from red color will be measured at 520nm wavelength and directly proportional to the uric acid concentration found in the serum sample. The reaction steps will be illustrated as follows:

(Uric acid + H_2O) $\xrightarrow{\text{Uricase}}$ (Allantoin + H_2O_2), then after Allantoin and H_2O_2 are formed, (H_2O_2 + phenolic compound + 4-amino-antipyrines) $\xrightarrow{\text{Peroxidase}}$ Red color quinonimine dye + H_2O

Procedure: About 20 microliter of serum sample was mixed in a cuvette with about 120mμ of R1 and 40mμ of R2 then incubated at 37°C for five minutes, or at room temperature for 15 minutes. The absorbance of light from the red color will be measured at 520nm wavelength and is proportional to the uric acid concentration found in the serum sample. The normal value of serum uric acid is SUA<6mg/dl.

2.6. Serum Creatinine

The alkaline picrate reacts with creatinine to form the orange-colored complex, which is read at 520 nm spectrophotometrically. The concentration is calculated using the following formula:

$$\text{SCr (mg/dl)} = \frac{absorbance \text{of the test} \times 2}{absorbance of standard}$$

Normal range of SCr is between 0.3-1.2 mg/dl.

2.7. Blood Urea Nitrogen

Principle: Urease catalyzes the conversion of urea to ammonia and carbon dioxide. Then, the released ammonia reacts with a mixture of salicylate, hypochlorite, and nitroprusside to yield indophenol, a blue-green colored compound. The intensity of the color produced is directly proportional to the concentration of urea in the sample and is measured at 578 nm spectrophotometrically.

$$\text{Urea (mg/dl)} = absorbance of substanse \times \frac{40}{absorbance\ of\ standard}$$

2.8. Estimated Glomerular Filtration Rate

GFR was estimated using the CKD-EPI formula using serum creatinine values, age, gender, and race. Estimated GFR was calculated by the 2009 CKD-EPI equation [33]. For females with, SCr≤ 0.7 mg/dl: GFR = 166 x (SCr/0.7) $^{-0.329}$ (0.993) ^{age} and females with, SCr> 0.7 mg/dl: GFR=166 × (SCr /0.7) $^{-1.209}$ x (0.993) $^{age.}$ For males with, SCr≤ 0.9 mg/dl: GFR=163 x (SCr / 0.9)$^{-0.411}$x (0.993) ^{age} and males with, SCr> 0.9 mg/dl: GFR=163 × (SCr / 0.9) $^{-1.209}$ x (0.993) $^{age.}$

The stages of eGFR are classified according to a classification system established by the National Kidney Foundation's Classification of the Kidney Disease Outcomes Quality Initiative (KDOQI). Stage-I=eGFR of ≥90 mL/min/1.73m^2, Stage-II=eGFR of 60-89 mL/min/1.73m^2, Stage-IIIA=eGFR of 45-59mL/min/1.73m^2, Stage-IIIB=eGFR of 30–44.9 mL/min/1.73 m^2, Stage-IV=eGFR of 15-29 mL/min/1.73 m^2, and Stage-V≤15 eGFR of mL/min/1.73 m^2.

2.9. Statistical Analysis

The collected data was entered to Epi data version 4.6 software and then exported to SPSS version 25 software for analysis. Kolmogorov-Shapiro Willi's test was used to check the continuity and normality of the data. Then, normally distributed data were put as mean ± standard deviation, while continuous and non-normal data are expressed as median. Categorical data were put as percentages. Pearson and Spearman's correlation was calculated to see the correlation between serum uric acid with various factors. Univariate and multivariate linear regression models were performed to test the significance of the association. Variables associated at p-value<0.05 were considered as statistically significant.

3. Result

3.1. Sociodemographic Characteristics of Study Participants

A total of one hundred forty study participants were recruited for this study. The mean age of study participants was 51.04 ± 9.02 years old. The majority of study participants were between the ages of 30-59 which accounts for 81.43% and 18.57% were greater or equal to sixty years old. Most of

the study participants were married (85.7%) whereas only 3.60% is unmarried. In terms of their occupation majority of the participants are farmers (66.40%), followed by merchants 18.60%. Majority of the study subjects were not alcohol consumer (93.6% [n=131]). The detail of sociodemographic characteristics depicted in below (Table 1).

Table 1. *Sociodemographic characteristics of study participants.*

Variables Categories		Frequency	Percentage
Sex:	Male	76	54.30
	Female	64	45.70
Age category	30-59 age group	114	81.43
	≥60 age group	26	18.57
Marital status:	Single	5	3.60
	Married	120	85.70
	Divorced	15	10.70
Occupation:	Farmer	93	66.40
	Merchant	26	18.60
	Gov'temployed	12	8.60
	Daily Labor	7	5.00
	Other	2	1.40
Smoking Status	Never smoke	125	89.30
	Former smoker	14	10.0
	Recent smoker	1	0.70
Alcohol Consumption	Yes	9	6.40
	No	131	93.60

3.2. Laboratory Measurements Result Among Participants

The mean value of serum uric acid was 7.2±2.1mg/dl. The mean of estimated glomerular filtration rate (eGFR) was 54.2±31 mL/min/1.73m^2. Furthermore, the mean values of serum creatinine and blood urea nitrogen among participants in this study were 3.2±1.4 and 67.8±35.8 mg/dL. The detail data available in below (Table 2).

Table 2. *The mean value of different laboratory result among participants.*

Variables	Mean ±SD
Serum uric acid	7.2±2.1 mg/dL
Serum creatinine	3.21±1.4 mg/dl)
Blood urea nitrogen	67.8±35.8 mg/dl)
Estimated glomerular filtration rate	54.2±30.31 mL/min/1.73m^2
Body mass index	23.7±1.87 kg/m^2
Systolic blood pressure	128.4±12.11 mmHg
Diastolic blood pressure	90.2±8.32 mmHg

Data are presented as mean ±SD

3.3. Clinical Data and Biochemical Parameters across CKD Stages

Among all study participants, (47.9% [n=105]) were known hypertensive and (25% [n=35]) had diagnosed diabetes mellitus (DM). In the recent study, only 6.4% had previous family history of kidney disease. A large number of CKD patients with known hypertension were found in stage IV (23.6% [n=33]), followed by stage III CKD (12.9% [n=18]) individuals with known hypertension individuals. Similarly, participants with pre-existing diabetes mellitus with (10.7% [n=15]) were found in stage-IV CKD followed by stage III with (5.7% [n=8]) known diabetic patients. In addition, values for systolic blood pressure, diastolic blood pressure, body mass index, estimated glomerular filtration rate, blood urea nitrogen, and serum creatinine increased with increasing chronic kidney disease stage (Table 3).

Table 3. *Distribution of various factors across CKD stages among study participants.*

Variables	Grouping of participants by CKD stage					
	Categories	Stage-I	Stage-II	Stage-III	Stag- IV	Stag- V
History of DM	Yes (N=35)	5 (3.6%)	3 (2.1%)	8 (5.7%)	15 (10.7%)	4 (2.9%)
	No (N=105)	16 (11.4%)	33 (23.6%)	26 (18.6%)	26 (18.6%)	4 (2.9%)
History of Hypertension	Yes (N=67)	4 (2.9%)	5 (3.6%)	18 (12.9%)	33 (23.6%)	7 (5.0%)
	No (N=73)	17 (12.1%)	31 (22.1%)	16 (11.4%)	8 (5.7%)	1 (0.7%)
Family History of Kidney diseases:	Yes (N=9)	1 (0.7%)	2 (1.4%)	0 (0%)	6 (4.3%)	0 (0%)
	No (N=131)	20 (14.3%)	34 (24.3%)	34 (24.3%)	35 (25%)	8 (5.8%)
Body Mass Index (kg/m^2)		22.16±1.7	22.69±1.38	22.82±1.71	22.65±1.57	23.91±0.9
Systolic Blood Pressure (mmHg)		120	119	128	130	135
Diastolic Blood Pressure (mmHg)		80	85.5	90.5	96	97
Serum Creatinine (mg/dl)		0.97	1.17	1.87	3.2	4.57
Blood Urea Nitrogen (mg/dl)		42.3±12.6	49.3±16.2	61.3±14.6	86.8±17.6	113.3±18
Serum Uric Acid (mg/dl)		4.5±0.50	5.4±0.95	7.4±0.56	9.3±0.86	10.5±1.67

DM: Diabetes Mellitus, eGFR: Estimated glomerular filtration rate.

3.4. Correlation Between Serum Uric Acid and Explanatory Variables

There was a significant negative correlation (r=-0.912 P=<0.001) between serum uric acid and eGFR among CKD patients. This indicates CKD patients who are in lower stages tend to have lower serum uric acid. A higher stages of CKD patients have a higher level of serum uric acid. There was a moderate positive correlation between systolic blood pressure, diastolic blood pressure, and age with serum uric acid in this study samples (Table 4).

The correlation between eGFR value and serum uric acid present below picture (Figure 1).

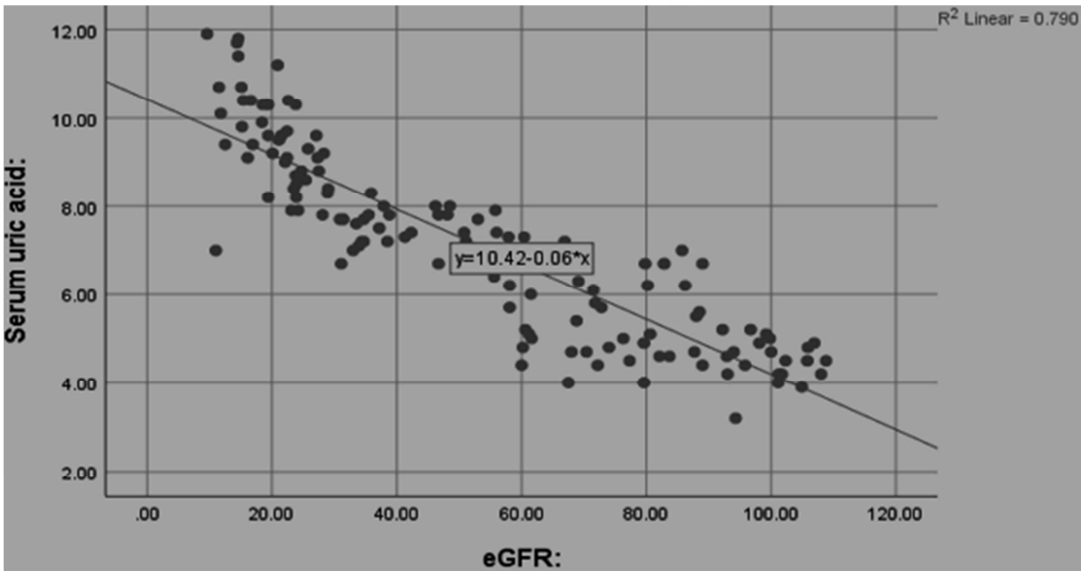

Figure 1. *Scatter plot shows the correlation between serum uric acid and eGFR among CKD patients.*

Table 4. *The correlation analysis between serum uric acid and different factors among CKD patients (N=140).*

Variable	Serum uric acid
	Spearman's correlation(r) P-value
eGFR	-0.912 <0.001*
SBP	0.584 <0.001*
DBP	0.481 <0.001*
AGE	0.4450 <0.001*

*Correlation is significant at p-value<0.05 (two-tailed).

3.5. Association of Serum Uric Acid with Dependent Variables

Univariate linear regression analysis was performed to test the association between a single explanatory variable and outcome variable (serum uric acid). In univariate linear regression analysis, factors included age (β=-0.071, p=0.006), history of hypertension (β=-0.006, p=0.0043), diabetes (β=-0.278, p=0.2973), systolic blood pressure (β=-0.094, p<0.001) and diastolic blood pressure (β=-0.0092, p<0.001) were positively associated with serum uric acid.

Then, the candidate variables are subjected to multiple linear regression. In multivariate linear regression, only two variables were significantly associated with uric acid in patients with CKD. The eGFR value was negatively associated with serum uric acid (β=-0.060, P=<0.003). However, systolic blood pressure had a positive association (β=-0.032, p=0.022) with serum uric acid (Table 5).

Table 5. *Factors associated with serum uric acid in CKD study participants.*

Lists of explanatory variables	Outcome variables (SUA) β (95% CI)	P-value (2-tailed)
Age (year)	0.001	0.866
History of HTN	0.006	0.431
History of DM	0.278	0.297
SBP (mmHg)	0.032	0.022*
DBP (mmHg)	0.022	0.772
eGFR (min/mL/1.73m^2)	-0.060	<0.003*

*Significant association at p-value <0.005

4. Discussion

The current finding is showing statistically significant correlation between eGFR and serum uric acid among CKD patients. Additionally in the recent study, eGFR is negatively and significantly associated (β=-0.060, P<0.003) with serum uric acid among CKD study participants. For every 1-unit increase in eGFR value, serum uric acid decreased by 0.06 among CKD patients.

This study revealed that serum uric acid is progressively increased with a decrease of eGFR in CKD patients. This study also found a moderate positive correlation (r=0.58, P<0.001, r=0.481, P<0.001) between serum uric acid and blood pressure (systolic and diastolic) in the study subjects respectively. A study done at the Medical University of Japan agrees with the recent finding. Their study found a significant negative correlation (r=−0.17, P<0.0001& r=−0.22, P<0.0001) between eGFR and SUA in both men and women respectively [34].

Another study finding from Shanghai (China), also support our finding and revealed a negative correlation (r=-0.415, P<0.001) between eGFR and SUA among CKD patients [35]. The result from the university of Tokyo, Japan, was consistent

with this finding and showed that eGFR was negatively associated (β=-0.367, p<0.05) with SUA in the CKD population. Another supporting result from the Thailand, subjects in the highest SUA quartile were significantly associated (OR 2.45; 95% CI) with rapid eGFR decline than those in the lowest quartile associated (OR 1.51; 95%CI) with eGFR decline [36]. According to another finding from Japan, SUA>6.0 mg/dL was a significantly associated (CI 95%, P<0.01) for rapid decline in eGFR [37].

The proposed mechanism was that uric acid decreases nitric oxide (NO) production and induces production of reactive oxygen species (ROS). Uric acid also activates mitogen-activated protein kinase and nuclear transcription factors that increase cyclooxygenase-2 production that exacerbate the damage of renal cell [37]. Decrease in production of endothelial NO and increase production of cyclooxygenase-2 cause's inflammation in the vascular endothelium, proliferation of vascular smooth muscle, and intrarenal vascular lesion. These overall cause activation of immune mechanisms in the kidney and related to CKD progression. Uric acid-also activation of RAAS results in renal vasoconstriction, inflammation of renal tubular cells ischemia, and oxidative stress [38].

Another similar finding was reported from the University of Thailand. According to their study, there was a negative and independent associations (β-0.21, P<0.001) between eGFR and change in the level of serum uric acid [22]. Elevated serum uric acid is potentially linked to increased vascular disease, microvascular changes leads to endothelial dysfunction, and renal tubular damage that fasten ESRD [22]. Another result from the University of Tokyo, Japan was agreed with this finding. The mean values of SUA were significantly different (6.46 ± 1.38 vs 6.53 ± 1.27 mg/dL, P =0.036) by student t-test at baseline and 2year later among CKD patients. Their study strongly suggested the beneficial effect of lowering SUA on slowing the progression of CKD and the target level of SUA may be less than 6.5 mg/dL [37].

In line with this study, the finding from Thailand, have reported a significant positive correlation (r=0.25, P<0.01) between serum uric acid and systolic blood pressure among the CKD study population. Furthermore, their study found the positive correlation (r=0.24, P<0.01) between serum uric acid and diastolic blood pressure [36].

In line to the recent finding, study from Korea association of health promotion, found the significant positive association (β=0.25, P=0.002) between systolic blood pressure and serum uric acid [39]. Study from Bangladeshi also support the current finding. According to their study, SUA concentrations were positively associated (P< 0.01) with SBP and SUA levels were increased positively in hypertension and prehypertension group compared to the normal blood pressure group in both sex groups [40].

The study done in China was contradictory to the current finding. According to that study, the correlation (r=0.005, P=0.858) between the decline in eGFR and increment of serum uric acid was not significant [41]. This variation may be due to differences in study design and study population. In the previous study, the design was prospective study design, and the study population was only stage-1 and stage-2 CKD patients in which serum uric acid increment is more likely mild.

5. Conclusion

According to the current findings, serum uric acid levels in patients with chronic kidney disease increased with increasing CKD stages. Estimated glomerular filtration rate was significantly and negatively correlated with serum uric acid value in CKD patients. Additionally, factors like age, systolic blood and diastolic blood pressure were significantly and positively correlated with serum uric acid level among chronic kidney disease. Furthermore, eGFR value was negatively associated with serum uric acid and whereas systolic blood pressure positively associated with serum uric acid. Therefore, increased age and high blood pressure are independent risk factors for disease progression in patients with CKD.

6. Limitation of This Study

A single measurement of serum samples might not be sufficiently accurate for confirming the correlation and association between outcome variables and explanatory variables. Since, the study subjects were recruited from a single hospital, the sample size might be small to the national target population.

7. Recommendations

The finding suggested to incorporate serum uric acid parameter as one of the routine laboratory tests to predict the progression of CKD disease. Additionally, further multicenter based studies with large sample sizes are needed to definitively examine the relationship between serum uric acid, eGFR and other variables.

List of Abbreviations

BMI: Body mass index
CKD: Chronic kidney disease
DM: Diabetes mellitus
eGFR: Estimated glomerular filtration rate
HTN: Hypertension
IL-1β: Interleukin one beta
IL-6: Interleukin six
TNF-α: Tomer necrosis factor alpha

Declaration

Authors' Contributions

Fikadu Seyoum Tola: is the rincipal investigator of this research and had full role in the research paper and manuscript preparation.

Belay Zawdie and Maekel Belay: Act as principal advisor

in guiding, commenting and contributed to manuscript editing activities.

Conflict of Interest

The authors declare that they have no competing interests.

Availability of Data and Materials

The dataset generated during/or analyzed during the current study are not publicly available due to the papers written using this dataset have not been published but are available from corresponding authors on reasonable request.

Ethical Approval and Consent for Participation

Before participating in the study, all the study subjects signed informed consent. The study was approved by Institutional Ethics review board (IERB) of the first affiliated Jimma University with IERB No. IHRPG1/6/2022. The study was conducted in accordance with the Helsinki declaration.

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