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CORRELATION BETWEEN GLOMERULAR FILTRATION RATE AND SERUM URIC ACID/CREATININE RATIO IN PRE-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS AT NGOERAH HOSPITAL DENPASAR

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ABSTRACT

Background: Chronic kidney disease (CKD) is a structural and functional kidney abnormalities for over three months. Glomerular filtration rate (GFR) is an index to measure overall kidney function. Decreased renal excretory function leads to elevated serum uric acid and serum creatinine levels. The serum uric acid/creatinine ratio is recently recognized as an indicator of kidney function deterioration. The purpose of this study to determine the correlation between GFR and serum uric acid/creatinine ratio in pre-dialysis CKD patients at Ngoerah Hospital Denpasar.
Methods: A cross-sectional analytical observational study was performed on 50 pre-dialysis CKD patients at Ngoerah Hospital Denpasar from 2022 to 2023, based on inclusion and exclusion criteria. The correlation between GFR and serum uric acid/creatinine ratio was assessed using Spearman's correlation test. The study participants were mostly male (68%), with a median age of 60.5 (21-79) years, and mostly in the stage G5 (74%). The median value of GFR was 16.85 (2.46-55.66) mL/min/1.73m^2 and the median value serum uric acid/creatinine ratio was 2.29 (0.39-7.49) mg/dL.
Results: The results of the correlation analysis between the GFR and serum uric acid/creatinine ratio was found r = 0.832 (p = 0.000).
Conclusion: This study conclude there was strong and significant positive correlation between GFR and serum uric acid/creatinine ratio.
Keywords : Chronic Kidney Disease, Glomerular Filtration Rate, Serum Uric Acid/Creatinine Ratio

INTRODUCTION

Chronic kidney disease (CKD) represents significant global health problems, affecting 8-16% of the world's population and as a leading cause of mortality in the 21st century[1]. Chronic kidney disease characterized by an abnormality in the structure and/or function of the kidneys persisting for more than 3 months, affecting the health[2]. The elimination of unused substances from the body is disrupted because of impaired kidney function, potentially leading to health complications, including hypertension, cardiovascular disease, stroke, and premature mortality[3].

In 2016, CKD was ranked as the 13th leading cause of death worldwide, and it expected to the 5th position by 2040 due to increasing prevalence[4]. The prevalence of CKD is various across several continents, attributed to the diverse in risk factors across populations. In the United States, the prevalence of CKD is significantly higher in the population aged 65 and above when compared to individuals in the 45-64 age group[3]. The prevalence of CKD stages G1-G5 in Europe varies from 3.31% in Norway and 17.3% in Northeast Germany[5]. In Asia, prevalence varies from 7% in South Korea to 34.3% in Singapore, with an estimated 434.3 million adults affected across East, South, and Southeast Asia[6]. According to Riset Kesehatan Dasar (Riskesdas), the prevalence of CKD in Indonesia has increased from 0.2% in

2013 to 0.38% in 2018, with similar trends observed in Bali province[7].

The Kidney Disease: Improving Global Outcome (KDIGO) guidelines classify CKD based on etiology, GFR, and albuminuria category. This classification system facilitates prognosis determination and treatment planning for CKD patients. Glomerular filtration rate is widely acknowledged as the best indicator of kidney function, as it typically declines with other kidney functions following structural damage[2]. It indicates the plasma flow rate from the glomerulus to the Bowman's capsule over a specified time period. A sustained GFR below 60 mL/min/1.73m^2 for more than three months is indicative of CKD[2,8]. Decreased GFR is associated with higher risk of CKD complications, such as metabolic and endocrine complications, drug toxicity, cardiovascular disease, and mortality[2].

Hyperuricemia, defined as uric acid levels exceeding 7 mg/dL in men and 6 mg/dL in women, is prevalent in approximately 80% of pre-dialysis stage 5 CKD patients[9]. This condition is also common in patients with hypertensive, type 2 diabetes mellitus, and cardiovascular disease due to increased oxidative stress and endothelial dysfunction, which contribute to reduced renal blood flow and GFR, ultimately increasing the risk of CKD development[10]. Research indicates that elevated serum uric acid levels are a risk factor for kidney disease progression and decreased estimated glomerular filtration rate (eGFR), suggesting that management of serum uric acid levels may mitigate kidney function deterioration[11]. Thus, hyperuricemia can be both a consequence of declining kidney function and a predictor of CKD onset. Given that excess uric acid often remains asymptomatic, routine screening for uric acid levels in CKD patients is crucial for preventing complications such as gout and kidney stone[12].

Recent research has identified a novel biomarker: the ratio of serum uric acid to serum creatinine levels, representing a normalized serum uric acid level in relation to kidney function. This ratio has been found to be indicative of decreased GFR or kidney dysfunction, potentially serving as a predictor of CKD. Additionally, the serum uric acid/creatinine ratio has been associated with metabolic syndrome[13–15]. However, conflicting evidence suggests that serum uric acid levels alone may be a superior indicator of kidney disorders in patients with diabetes mellitus[16]. Similar findings indicate that the serum uric acid/ creatinine ratio may not be reliably associated with CKD in hypertensive patients[17]. Other studies propose that the ratio between serum uric acid and serum creatinine levels may provide a more accurate representation of endogenous uric acid levels compared to serum uric acid levels its selves[13]. This ratio could assist healthcare providers in differentiating between hyperuricemia caused by excessive production and that resulting from reduced excretion due to compromised renal function, facilitating more effective monitoring of kidney function deterioration. Given the disparities in these research findings, the author proposes to investigate the correlation between glomerular filtration rate and the serum uric acid/creatinine ratio in pre-dialysis CKD patients.

METHODS

This analytical observational study employed a cross-sectional design and received ethical approval [2024.01.1.0120] from The Research Ethics Committee, Faculty of Medicine, Udayana University. The study population included pre-dialysis CKD patients with undergoing treatment at Ngoerah Hospital Denpasar during 2022-2023, who fulfilled specific inclusion and exclusion criteria. Inclusion criteria included patients diagnosed with CKD, without prior dialysis treatment, aged 18 or above, and with concurrent records of GFR, serum uric acid levels, and serum creatinine levels. Exclusion criteria involved patients with incomplete medical records or a history of tumor lysis syndrome or leukemia.

The research was conducted from March to August 2024 at the Medical Record Installation of Ngoerah Hospital Denpasar. Consecutive sampling was used to obtain a final of 50 eligible patients. Data extracted from medical records included GFR, serum uric acid levels, and serum creatinine levels. Descriptive analysis was performed on all collected data, with results presented as mean ± standard deviation (SD) for normally distributed data and median (minimum-maximum) for non-normally distributed data. The Shapiro-Wilk test was used to assess data normality, with a p-value >0.05 indicating normal distribution. The correlation between GFR and the serum uric acid/creatinine ratio was evaluated using the Spearman correlation test, given the non-normal distribution of the data (with significance level of $\alpha = 0.05$).

RESULTS

Table 1 presents the characteristics of participants in this study. The median age of patients is 60.5 years, within 21-79 years age range. The participants are mostly males (68%, n = 34) dan mostly at the G5 stage of CKD (74%, n = 37).

Table 1. Characteristics of pre-dialysis CKD patients

Characteristic	n (%)	Median (min-max)
Age (years)		60,5 (21-79)
Sex		
Female	16 (32)	
Male	34 (68)	
Staging of CKD:		
Stage 2 (60-89)	1 (2)	
Stage 3a (45-59)	1 (2)	
Stage 3b (30-44)	3 (6)	
Stage 4 (15-29)	8 (16)	
Stage 5 (<15)	37 (74)	

Note: CKD = chronic kidney disease

Table 2 presents the characteristics of GFR, serum uric acid, serum creatinine, and serum uric acid/creatinine ratio values for the study participants. The median GFR value among the 50 pre-dialysis CKD patients was 16.85 mL/min/1.73m^2, ranging from 2.46 to 55.66 mL/min/1.73m^2. Elevated serum uric acid levels were observed in 80% of subjects (n = 40), while 20% (n = 10) exhibited normal levels. No patients presented with low serum uric acid levels. The mean ± SD of serum uric acid level was 7.97 ± 1.91 mg/dL.

Serum creatinine levels ranged from 1.20 to 20.21 mg/dL, with a median of 3.38 mg/dL. The serum uric acid/creatinine ratio varied from 0.39 to 7.49 mg/dL, with a median of 2.29 mg/dL. Most patients (78%, n = 39) demonstrated low serum uric acid/creatinine ratio (<3.18 mg/dL), indicating a higher risk of renal function decline. Conversely, 22% of patients (n = 11) exhibited a serum uric acid/creatinine ratio exceeding 3.18 mg/dL, suggesting a lower risk of renal function regressivity. When grouped by CKD stage, the average distribution of serum uric acid/creatinine ratio in this study showed a decreasing trend in stages G3b, G4, and G5, corresponding with a decrease in GFR: G3b stage at 4.87 ± 1 mg/dL, G4 at 2.5 ± 0.54 mg/dL, and G5 at 1.87 ± 1.05 mg/dL as shown in **Figure 1**.

Table 2. GFR, serum uric acid, serum creatinine, and serum uric acid/creatinine ratio value of pre-dialysis CKD patients

Parameter	Mean ± SD	Median (min-max)	Normality test (p-value)*
GFR (mL/min/ 1.73m^2)		16.85 (2.46-55.66)	<0.05
Serum uric acid levels (mg/dL)	7.97 ± 1.91		>0.05
Serum creatinine levels (mg/dL)		3.38 (1.20-20.21)	<0.05
Serum uric acid/creatinine ratio (mg/dL)		2.29 (0.39-7.49)	<0.05

Note: GFR = glomerular filtration rate
*Based on Shapiro-Wilk test

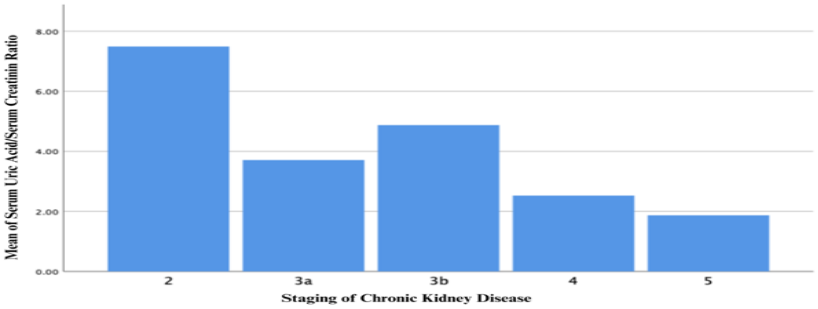

Figure 1. Mean serum uric acid/creatinine ratio trend bar chart

Table 3 presents the correlation between GFR values and the serum uric acid/creatinine ratio in pre-dialysis CKD patients. The correlation was assessed using the Spearman correlation test due to non-normal data distribution. The strength of correlation (*r*) is interpreted as follows: very weak (0.0 - <0.2), weak (0.2 - <0.4), moderate (0.4 - <0.6), strong (0.6 - <0.8), and very strong (0.80 - 1.00). The analysis revealed a very strong, statistically significant positive correlation between GFR values and the serum uric acid/creatinine ratio. The correlation coefficient was $r = 0.832$ ($p = 0.000$). This finding indicates GFR value increases as serum uric acid/creatinine ratio increases.

Table 3. Correlation of GFR value with serum uric acid/creatinine ratio in pre-dialysis CKD patients

Correlation	Correlation coefficient	p-value
GFR with serum uric acid/creatinine ratio	0,832**	0,000

Note: GFR = glomerular filtration rate
**Significant

DISCUSSION

This study encompasses 50 patients with pre-dialysis chronic kidney disease (CKD) who fulfill the specified inclusion and exclusion criteria. In comparison, Mantiri et al. conducted research with 35 patients with stage 5 pre-dialysis CKD[9]. Conversely, other studies utilized larger sample sizes: Pelupessy et al. with 64 pre-dialysis CKD patients, Moula et al. with 82 pre-dialysis CKD patients, and Nivedita et al. with 140 CKD patients)[18–20]. The age range of the research subjects in this study spans from 21 to 79 years, with a median age of 60.5 years. Most participants belong within the 60 to 69 years age bracket. These findings align with previous research, such as Moula et al. which reported the highest age group distribution of pre-dialysis CKD patients as 65-86 years old, and Pelupessy et al. which noted the highest distribution in the 56 to 65 years range[18,19]. Strengthen these results, data from the Ministry of Health of the Republic of Indonesia indicates that the highest prevalence of CKD occurs in the 65 to 74 years age group[21]. The higher incidence of CKD in older populations can be attributed to age-related changes in kidney structure, physiological alterations, and an increased risk of comorbid conditions such as hypertension, obesity, and diabetes. These factors are associated with a decline in GFR, indicative of reduced kidney function[22,23].

This study found that males comprised 68% of the subjects, while females accounted for 32%. Research by Made et al. and Moula et al. also reported a higher proportion of male pre-dialysis CKD patients, at 57.9% and 65.85% respectively[19,24]. This trend aligns with the gender-based prevalence of CKD in Singapore and Japan. According to Riskesdas data from the Indonesian Ministry of Health the prevalence of CKD in males is higher, at 0.42% of the total Indonesian population[21]. However, in countries such as France, Thailand, Portugal, and Turkey, women have a higher prevalence of CKD[25]. These gender differences can be attributed to hormonal and lifestyle factors. Estrogen in women tends to protect podocytes from apoptosis, while testosterone triggers apoptosis through an androgen receptor-dependent mechanism. During menopause, as estrogen levels decrease, women lose this podocyte protection, leading to a higher prevalence of CKD in menopausal women[26–28]. In men, increased protein consumption can elevate testosterone levels, potentially damaging the kidneys[28]. Additionally, poor lifestyle choices such as smoking, alcohol consumption, and unhealthy eating habits contribute to a faster decline in kidney function across both genders[25].

The distribution of CKD stage diagnosis according to KDIGO in this study is predominantly in the G5 stage (74%), with a GFR <15 mL/min/1.73m². The GFR values in this study had a median of 16.85 mL/min/1.73m² with a range of 2.46–55.66 mL/min/1.73m². This prevalence is due to the research being conducted at the Ngoerah Hospital Denpasar, a referral center for smaller health facilities. Furthermore, limited access to early treatment, delayed diagnosis, and presence of comorbidities or complications may explain why CKD patients at this hospital are more commonly found in an advanced stage.

This study found that 40 (80%) pre-dialysis CKD patients had high serum uric acid levels. This result aligns with a study by Mantiri et al. (2017), which reported increased serum uric acid levels in 80% of 35 pre-dialysis CKD patients[9]. In our study, the average serum uric acid level of pre-dialysis CKD patients was 7.97 ± 1.91 mg/dL. Barman et al. reported a lower average of 5.8 ± 1.6 mg/dL, with a maximum of 11.8 mg/dL[29]. Conversely, Moula et al. found a higher average of 10.07 ± 3.15 mg/dL, with a maximum of 19.9 mg/dL[19]. The high prevalence of hyperuricemia in pre-dialysis CKD patients observed in this study may be attributed to renal aging in elderly individuals. Reduced nephron count and kidney function in the elderly lead to inadequate uric acid filtration, causing uric acid accumulation in the blood[30]. Gu et al. found that serum uric acid levels were higher in advanced CKD stages (G3 or above)[15]. Consequently, patients with low GFR values are more likely to have elevated serum uric acid levels and a higher risk of kidney disease. Studies by Moula et al. and Pelupessy et al. strengthen these findings, demonstrating a negative correlation between GFR values and serum uric acid levels—as GFR decreases, serum uric acid levels increase[18,19].

In this study, the median ratio of uric acid to creatinine levels in serum was 2.29 mg/dL (ranging from 0.39–7.49 mg/dL). Our findings showed that 39 (78%) pre-dialysis CKD patients had a low serum uric acid/creatinine ratio (<3.18 mg/dL), indicating a risk of high renal function regressivity. When grouped by CKD stage, the average distribution of serum uric acid/creatinine ratio in this study showed a decreasing trend in stages G3b, G4, and G5, corresponding with a decrease in GFR: G3b stage at 4.87 ± 1 mg/dL, G4 at 2.5 ± 0.54 mg/dL, and G5 at 1.87 ± 1.05 mg/dL.

In this study, there was a very strong and significant positive correlation between the GFR value and serum uric acid/creatinine ratio, with a correlation coefficient of $r = 0.832$ ($p = 0.000$). These findings align with research by Gu et al. Ephraim et al. and Silva et al. which also found positive and significant correlations between GFR values and serum uric acid/creatinine ratio[15–17]. Ephraim et al. observed a decrease in the serum uric acid/creatinine ratio as CKD progressed[16]. As CKD advances, uric acid and creatinine accumulate in the blood due to impaired renal excretory function. These compounds, as indices of these ratios, were independently associated with an increased risk of kidney disease progression[15]. The declining of serum uric acid/creatinine ratio reflects the kidneys' decreasing ability to remove waste products efficiently[16]. As creatinine accumulates, it can trigger other diseases such as hypertension, anemia, and bone damage[31].

Kidney function affects uric acid excretion, leading to the development of a new biomarker: the serum uric acid/creatinine ratio. This ratio reflects uric acid production and provides a clearer picture of the kidney's excretory ability[14]. Beyond its association with decreased kidney function, this ratio is also linked to various health risks. These include metabolic syndrome (characterized by central obesity, hyperglycemia, hypertriglyceridemia, low HDL cholesterol, and hypertension), metabolic-associated fatty liver disease (MAFLD), cardiovascular disease, and diabetic kidney disease (DKD)[13,32–35]. Given these connections, regular monitoring of serum uric acid/creatinine ratio is crucial for pre-dialysis CKD patients. The strong positive correlation between GFR values and the serum uric acid/creatinine ratio offers a simpler way to assess the rate of kidney function decline.

CONCLUSION

This study concludes that there is a strong, significant positive correlation between GFR and serum uric acid/creatinine ratio. This correlation indicates that a decrease in GFR is accompanied by a decrease in the serum uric acid/creatinine ratio in patients with pre-dialysis CKD. These findings can inform the management of hyperuricemia and hypercreatinemia in pre-dialysis CKD patients. Further research is needed, involving a larger sample size across multiple hospitals. Future studies should also consider factors such as body mass index (BMI), lifestyle, metabolism, and diet to establish a stronger correlation between GFR values and serum uric acid/creatinine ratio.

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