Original Article

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Biochemistry Section

Altered Mineral Metabolism, Serum Uric Acid to Creatinine Ratio and Atherogenic Index of Plasma as Cardiovascular Risk Predictors in Chronic Kidney Disease: A Cross-sectional Study

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ABSTRACT

Introduction: Chronic Kidney Disease (CKD) is a significant public health issue associated with increased cardiovascular morbidity. Mineral metabolism imbalance and dyslipidaemia exacerbate Vascular Calcification (VC) and cardiac dysfunction. Serum Uric Acid to Creatinine Ratio (UACR) and Atherogenic Index of Plasma (AIP) have been explored as biomarkers for cardiovascular risk in CKD; however, limited data is available in this regard.

Aim: The study aimed to evaluate the utility of UACR and AIP as cardiovascular risk factor and also to study the correlation of CKD stages with UACR, AIP, lipid profiles, and mineral metabolism in CKD patients.

Materials and Methods: A cross-sectional study was conducted from December 2013 to June 2016 at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India. The study included 50 CKD patients and 50 healthy controls. CKD diagnosis was confirmed using Kidney Disease: Improving Global Outcomes (KIDGO) criteria. Participants included adults aged 18-70 years with confirmed CKD stages 3-5 who provided informed consent. Data on demographics, serum uric acid, creatinine, lipid profiles, calcium, and phosphate levels were collected. UACR and AIP were calculated. Statistical analyses—including Independent t-tests, Chi-square tests, and Pearson correlation analyses—were performed, with a statistical significance of p-value <0.05.

Results: The mean age of CKD patients was 47.74±11.01 years, with a male predominance (62%). From Stage 3 to Stage 5 CKD, lipid profiles deteriorated significantly with TC/HDL-C ratio increasing from 3.45 to 4.05 (p-value <0.001) and TG/HDL-C from 2.55 to 5.55 (r-value=0.70, p-value <0.001). AIP increased from 0.04 to 0.26 (p-value <0.001), while UACR showed negative correlation (r-value=-0.30, p-value=0.05) with lipid parameters. Calcium-phosphorus product showed a strong correlation with CKD progression (r-value=0.62, p-value <0.001). Renal function declined with elevated blood urea (119.88 to 190.45 mg/dL, p-value <0.001) and creatinine levels (7.04 to 10.76 mg/dL, p-value <0.001).

Conclusion: UACR and AIP are effective predictors of cardiovascular risk in CKD patients, correlating with dyslipidaemia and declining renal function. These findings support their use in risk stratification and management in CKD care.

Keywords: Cardiovascular biomarkers, Dyslipidaemia, Mineral bone disorder, Renal impairment, Vascular calcification

INTRODUCTION

The CKD represents a growing public health challenge worldwide, with particular concern in India [1]. The estimated prevalence of CKD in the Indian population is approximately 17%, with higher rates in urban areas, placing a substantial burden on the healthcare system and underscoring the urgent need for effective screening and management strategies [1]. The mechanisms underlying mineral metabolism disturbances in CKD involve complex interactions among parathyroid hormone, vitamin D, Fibroblast Growth Factor-23 (FGF-23), and klotho, resulting in disrupted calcium-phosphate homeostasis [2]. These disturbances contribute to VC through active cellular processes, including the osteogenic transformation of vascular smooth muscle cells [3]. Among these contributing factors, elevated calcium-phosphate product (Ca×P product) has been recognised as a key risk marker [4]. Hypercalcaemia can raise the Ca×P product, promoting precipitation of calcium-phosphate complexes in vascular tissues and accelerating the progression of VC [5].

CKD patients exhibit a higher prevalence of VC compared to the general population, contributing to an elevated risk of cardiovascular morbidity and mortality [6]. CKD-Mineral and Bone Disorder (CKD-MBD) refers to an imbalance in mineral and bone metabolism resulting from CKD, with increased serum calcium and phosphate levels considered major risk factors for the development of VC in these patients [7]. Hypercalcaemia is suggested to contribute to VC by increasing the Ca×P product [8,9].

Among the metabolic disturbances commonly seen in CKD, dysregulation of uric acid and lipid metabolism plays a critical role in disease progression and adverse cardiovascular outcomes [10]. Elevated serum uric acid levels, for instance, have been associated with oxidative stress and inflammation, both of which exacerbate renal damage and increase cardiovascular risk [11,12]. The serum UACR thus emerges as a potential biomarker for assessing renal function and predicting mortality in CKD populations [13,14]. Studies have shown that higher UACR is linked to an elevated risk of cardiovascular events, reflecting the underlying inflammatory processes common in CKD patients [15,16].

The AIP, calculated as the logarithmic ratio of triglycerides to HDL-cholesterol, has garnered attention as an effective measure of cardiovascular risk, particularly in CKD patients [17,18]. Dyslipidaemia is not only a marker of CKD progression but also a key contributor to VC and atherosclerotic plaque formation [19,20]. High AIP levels indicate an atherogenic lipid profile, which can lead to endothelial dysfunction and increase the likelihood of cardiovascular events in CKD patients [21]. Monitoring AIP in conjunction with UACR could,

therefore, provide meaningful insights into cardiovascular and renal health, aiding in the development of more tailored and effective management strategies.

Previous studies have extensively investigated various biomarkers for cardiovascular risk prediction in CKD patients. However, there remains a gap in understanding the combined utility of UACR and AIP as comprehensive cardiovascular risk predictors. While individual studies have examined uric acid metabolism [22,23] and lipid abnormalities [24] separately, limited research has explored their synergistic relationship in CKD progression [25-28]. The present study addresses this lacuna by simultaneously evaluating both biomarkers across different CKD stages, providing novel insights into their comparative effectiveness for cardiac risk stratification.

This study aimed to assess the effectiveness of the serum UACR and the AIP as predictors of cardiovascular risk in patients with CKD, and to study the impact of elevated calcium-phosphate products. This approach was expected to enhance risk stratification in clinical practice, ultimately improving outcomes for CKD patients.

MATERIALS AND METHODS

A cross-sectional study was conducted at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India from December 2013 to June 2016. Ethics clearance was obtained from the Institutional Ethics Committee on November 30, 2013 (IEC Approval No. VIMS/RC/IEC/103/2013-14). Patients who provided written informed consent were enrolled.

Inclusion criteria: Male and female adults aged 18-70 years diagnosed with CKD stages 3-5 according to KDIGO criteria (estimated Glomerular Filtration Rate [eGFR] <60 mL/min/1.73 m^2 for >3 months) were included as cases.

a. **Stage 3a:** eGFR 45-59 mL/min/1.73 m^2 - mild to moderate decrease in kidney function.
b. **Stage 3b:** eGFR 30-44 mL/min/1.73 m^2 - moderate to severe decrease in kidney function.
c. **Stage 4:** eGFR 15-29 mL/min/1.73 m^2 - severe decrease in kidney function.
d. **Stage 5:** eGFR <15 mL/min/1.73 m^2 - kidney failure (dialysis or transplant needed) [29].

All CKD stages required an eGFR <60 mL/min/1.73 m^2 persisting for >3 months with evidence of kidney damage.

Controls included male and female adults aged 18-70 years with eGFR ≥60 mL/min/1.73 m^2 for at least three months (i.e., not diagnosed with CKD stages 3-5), based on KDIGO guidelines, absence of proteinuria or haematuria on urinalysis.

Exclusion criteria: Patients with acute kidney injury, malignancies, autoimmune diseases, or other chronic illnesses that may affect kidney function or lipid profiles were excluded. Patients currently undergoing dialysis or who had undergone kidney transplantation were also excluded. Subjects using lipid-lowering, antihypertensive, or uric acid-modifying drugs within the past three months. Pregnant or lactating women, were also excluded from the study.

Sample size: The sample size was calculated using the following formula for comparing two means [30].

$n=2\sigma^2(Z\alpha/2+Z\beta)^2/(\mu1-\mu2)^2$

Where:

- σ=3.11 (standard deviation).
- $Z\alpha/2$=1.96 (95% confidence level).
- $Z\beta$=0.84 (80% power).
- $\mu1$=9.6 (expected mean for cases).
- $\mu2$=adjusted mean for controls.

The calculated sample size was 50 participants per group, totaling 100 participants.

Data collection: Data were collected from patients visiting the Medicine and Nephrology Outpatient Departments (OPDs), inpatient wards, and through patient interviews.

Laboratory measurements were performed using the methods given in [Table/Fig-1,2] [17,29-33].

Parameter	Method of Estimation	Normal/Reference Range
Serum creatinine	Jaffe kinetic method	0.6-1.2 mg/dL [30]
Serum uric acid	Uricase enzymatic method	3.5-7.2 mg/dL [30]
Serum calcium	Arsenazo III method	8.5-10.5 mg/dL [30]
Serum phosphorus	Phosphomolybdate method	2.5-4.5 mg/dL [30]
Triglycerides (TG)	GPO-PAP enzymatic method	<150 mg/dL [30]
HDL-Cholesterol (HDL-C)	Direct enzymatic method	>40 mg/dL (men), >50 mg/dL (women) [30]

[Table/Fig-1]: Method of estimation and cut-off range for the lab parameters [30].

Derived parameter	Formula/calculation	Interpretation/Cut-off
eGFR	CKD-MDRD equation	CKD stage classification based on eGFR [29,31]
Atherogenic Index of Plasma (AIP)	$\log_{10}$ (TG/HDL-C) (lipids in mmol/L)	<0.1: Low-risk; 0.1-0.24: Intermediate; >0.24: High-risk [17]
Uric Acid-to-Creatinine Ratio (UACR)	Uric acid (mg/dL)÷Creatinine (mg/dL)	No fixed cut-off; compared across CKD stages [32]
Calcium-Phosphorus Product	Serum Calcium×Serum Phosphorus (mg^2/dL^2)	Typically <55 mg^2/dL^2 to reduce Vascular Calcification (VC) risk [33]

[Table/Fig-2]: Method of estimation and cut-off range for derived parameters [17,29,31-33].

Dyslipidaemia classification: Lipid levels were interpreted using the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) guidelines [34].

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 23.0; IBM Corp., Armonk, NY, USA). Data were expressed as mean±Standard Deviation (SD) for continuous variables and percentages for categorical variables. The t-test was utilised to compare the CKD and non CKD groups. Pearson's correlation analysis was employed to evaluate the correlation between AIP and other variables. A p-value of <0.05 was considered statistically significant.

RESULTS

In the present study, both groups showed male predominance compared to females. Most CKD cases, 30 (60%), were in stage 5, while controls had no CKD [Table/Fig-3]. Although a small number of patients were initially classified under CKD stages 1 and 2, they were excluded from final analysis.

Characteristic	Cases (n=50)	Controls (n=50)	p-value
Age (years)	47.74±11.01 (50, 100%)	45.66±11.46 (50, 100%)	0.364
Gender			
Male	31 (62.0%)	34 (68.0%)	0.529
Female	19 (38.0%)	16 (32.0%)	
CKD Stage			
Stage 1	4 (8.0%)	0	-
Stage 2	4 (8.0%)	0	
Stage 3	4 (8.0%)	0	
Stage 4	8 (16.0%)	0	
Stage 5	30 (60.0%)	0	

[Table/Fig-3]: Baseline characteristics of study population.
*Statistical note: Independent t-test was applied for continuous variables (age); Chi-square test/ Fisher's exact test was used for categorical variables (gender)

The CKD patients demonstrated significantly impaired renal function, with reduced eGFR and elevated uremic toxins. Disturbances in mineral metabolism were evident, including hypocalcaemia, hyperphosphatemia, and elevated Ca×P product, indicating an increased VC risk [Table/Fig-4].

Parameters	Cases (n=50)	Controls (n=50)	p-value
eGFR (mL/min)	14.12±10.72	102.97±27.46	<0.001**
Serum urea (mg/dL)	119.88±71.29	23.67±5.76	<0.001**
Serum creatinine (mg/dL)	7.04±5.34	0.84±0.20	<0.001**
Serum calcium (mg/dL)	8.11±1.09	9.31±0.42	<0.001**
Serum phosphorus (mg/dL)	4.86±1.83	3.27±0.54	<0.001**
Ca×P ionic Product	58.99±13.77	30.46±5.03	<0.001**
Serum magnesium (mg/dL)	2.00±0.51	1.91±0.30	0.267
Uric Acid to Creatinine Ratio (UACR)	1.10±0.40	6.20±1.90	<0.001**
TC/HDL-C Ratio	5.20±1.10	3.60±0.80	<0.001**
TG/HDL-C Ratio	4.10±1.20	2.10±0.70	<0.001**
LDL-C/HDL-C Ratio	3.20±0.90	2.00±0.60	<0.001**
Atherogenic Index of Plasma (AIP)	0.35±0.10	0.12±0.08	<0.001**
TC (mg/dL)	195.40±42.50	172.60±35.40	0.006**
HDL (mg/dL)	32.20±8.10	47.30±9.20	<0.001**
TG (mg/dL)	180.50±60.40	115.20±32.70	<0.001**
LDL (mg/dL)	115.40±35.20	102.10±28.60	0.041*

[Table/Fig-4]: Comparison of renal and mineral biomarkers between CKD cases and controls.

As CKD progressed from Stage 3 to Stage 5, TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C ratios, along with AIP and Calcium×phosphate product, all increased significantly (p-value <0.001), indicating worsening lipid profile and higher cardiovascular risk. UACR decreased in Stage 5 compared to earlier stages, with borderline significance (p-value=0.05), possibly reflecting altered kidney excretion or muscle mass changes [Table/Fig-5].

Parameter	Stage 3 (n=4)	Stage 4 (n=8)	Stage 5 (n=30)	p-value
TC/HDL-C ratio	3.45±1.15	3.05±0.55	4.05±0.55	<0.001
TG/HDL-C ratio	2.55±1.65	3.25±0.15	5.55±2.05	<0.001
LDL-C/HDL-C ratio	1.95±0.65	2.25±0.55	2.75±0.85	<0.001
Atherogenic Index of Plasma (AIP)	0.04±0.12	0.19±0.15	0.26±0.12	<0.001
Uric Acid to Creatinine Ratio (UACR)	0.77±0.15	0.88±0.17	0.56±0.20	0.050
Calcium×Phosphate Product	36.00±12.75	42.50±13.05	54.00±14.55	<0.001
Total Cholesterol (TC, mg/dL)	188.5±28.0	192.0±30.5	198.0±40.0	0.041*
HDL (mg/dL)	41.5±6.0	36.5±5.5	30.5±7.0	<0.001
Triglycerides (TG, mg/dL)	140.0±25.5	165.0±30.0	190.0±40.0	<0.001
LDL (mg/dL)	108.0±20.5	112.5±25.0	118.0±30.5	0.048*
Serum urea (mg/dL)	62.0±15.5	98.0±20.5	135.0±35.5	<0.001
Serum creatinine (mg/dL)	2.80±0.65	5.10±1.25	8.20±2.75	<0.001
Serum calcium (mg/dL)	8.90±0.50	8.30±0.60	7.95±0.80	<0.001
Serum phosphorus (mg/dL)	4.10±0.60	4.55±0.75	5.10±1.10	<0.001
Serum magnesium	1.95±0.25	2.25±0.35	2.65±0.40	<0.001

[Table/Fig-5]: Lipid ratios, AIP, UACR, and calcium×phosphate product across CKD stages.

Pearson correlation analysis revealed strong positive associations between lipid-related indices and the outcome variable. The TG/HDL-C ratio showed the highest correlation (r-value=0.70, p-value <0.001), followed by TC/HDL-C (r-value=0.65), AIP (r-value=0.65), and LDL-C/HDL-C (r-value=0.60), all statistically significant. The calcium×phosphate product also demonstrated a moderate positive correlation (r-value=0.62, p-value <0.001), indicating possible involvement of mineral metabolism. In contrast, the UACR showed a moderate negative correlation (r-value=-0.30, p-value=0.05), suggesting a limited association [Table/Fig-6,7].

Parameter	Pearson r	p-value	Significance
TC/HDL-C Ratio	0.65	<0.001	Highly significant
TG/HDL-C Ratio	0.70	<0.001	Highly significant
LDL-C/HDL-C Ratio	0.60	<0.001	Highly significant
Atherogenic Index of Plasma (AIP)	0.65	<0.001	Highly significant
Uric Acid to Creatinine Ratio (UACR)	-0.30	0.05	Marginally significant
Calcium × Phosphate product	0.62	<0.001	Highly significant

[Table/Fig-6]: Correlation of lipid ratios, AIP, UACR, and Calcium×Phosphate product with CKD stage.

DISCUSSION

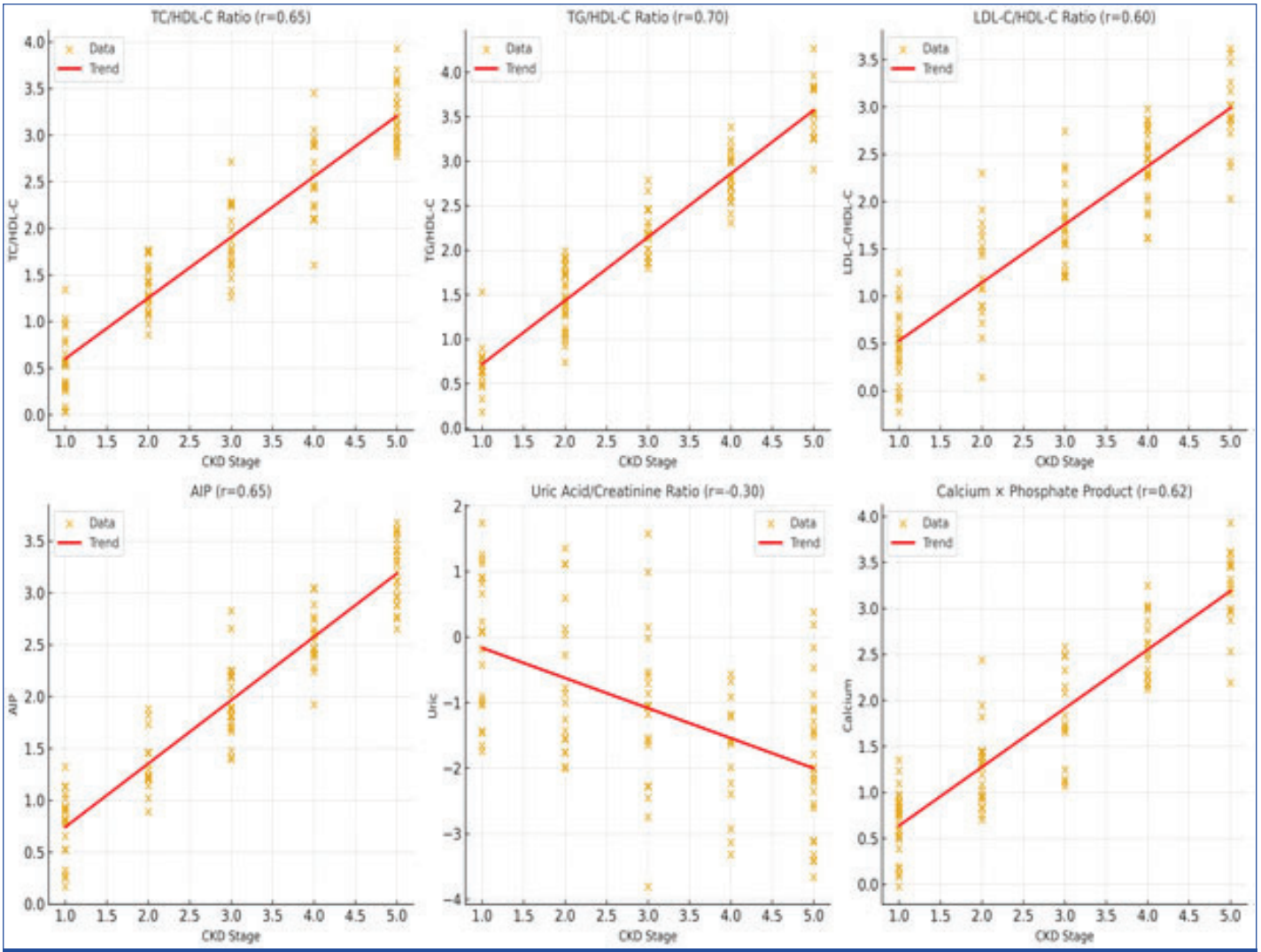
The current study demonstrated a significant positive correlation between the AIP and CKD stage, highlighting a trend of worsening dyslipidaemia and escalating cardiovascular risk as renal function deteriorated. This observation was consistent with findings by Li H et al., who identified AIP as an early biomarker for CKD and liver injury, particularly among diabetic populations [21]. Their study emphasised that elevated AIP values could be detected even before overt renal impairment became clinically apparent, underlining AIP's potential for early risk stratification.

Wang B et al., further supported the association between AIP and CKD through their analysis of a large, nationally representative sample [18]. They reported a non linear relationship between AIP and CKD prevalence, suggesting that even modest elevations in AIP were associated with increased odds of CKD, although their findings indicated more complex interactions than a simple linear progression. In contrast, the current study observed a steady, linear increase in AIP levels with advancing CKD stages, reflecting a continuous aggravation of lipid abnormalities.

In a Korean population-based cohort, You F et al., reported that AIP was independently predictive of both all-cause and cardiovascular mortality [19]. These findings echoed the current study's results, where AIP progressively rose from CKD stage 3 to stage 5, highlighting its potential as a prognostic biomarker for long-term outcomes. Zhang J et al., similarly demonstrated that AIP served as a risk factor for future cardiovascular events in early-stage CKD [20]. The present study extends this prognostic utility to patients with advanced CKD, emphasising the continuous relevance of AIP throughout disease progression.

Hu Y et al., reported that a higher atherogenic index of plasma was significantly associated with increased cardiovascular disease risk across cardiovascular-kidney-metabolic syndrome stages 0-3, while Ghanavatian S et al., demonstrated that endothelial dysfunction and subclinical atherosclerosis are prominent features in patients with stage 3-4 chronic kidney disease, supporting a mechanistic link between AIP and cardiovascular morbidity in CKD [22,23]. Their findings support the concept that atherogenic dyslipidaemia, as indexed by AIP, plays a central role in mediating vascular complications in CKD patients.

The present study also observed significant elevation of the calcium-phosphate (Ca×P) product in CKD stages 4 and 5, which aligns with previous research on mineral bone disorders in CKD. Siracusa C et al., and Shanahan CM et al., described the mechanisms by which deranged calcium and phosphate metabolism contribute to VC, including the transformation of vascular smooth muscle cells into osteoblast-like cells [2,3]. Kostov K et al., proposed the Ca×P/eGFR ratio as a sensitive marker of cardiovascular risk in predialysis



[Table/Fig-7]: Correlation of cardiometabolic and biochemical parameters with target variable: Pearson r and significance.

CKD patients [4]. This was further corroborated by findings from Fernandez L and Klein J, and Block GA et al., who linked elevated Ca×P levels with higher mortality and vascular complications [5,10].

Lastly, the UACR demonstrated a negative correlation with CKD stage in this study, suggesting declining uric acid excretion or changes in muscle mass with advancing disease. Silva NR et al., reported that higher UACR values were independently associated with increased long-term mortality risk [13]. Elevated uric acid is associated with increased cardiovascular risk and mortality in CKD [11], while uric acid-lowering therapy shows limited effect on endothelial function [12], and AIP serves as an early marker of CKD and liver injury in type 2 diabetes [21].

Limitation(s)

This study had several limitations that should be acknowledged. The cross-sectional design limits the ability to establish causal relationships. Although the sample size of 100 participants was adequate for the primary objectives, it may limit generalisability. The single-centre design may introduce selection bias and limit external validity. Confounding factors such as dietary patterns, medication use, and physical activity were not systematically evaluated. Additionally, the study did not include CKD stages 1 and 2 limiting the assessment of biomarker utility across the complete CKD spectrum.

CONCLUSION(S)

This study highlights a significant association between advancing CKD stages and rising AIP, lipid ratios, and calcium-phosphate product, indicating worsening dyslipidaemia, mineral imbalance, and increased cardiovascular risk. The negative correlation of UACR with CKD stage may reflect impaired renal excretion and declining muscle mass. These findings underscore the clinical utility of AIP, lipid ratios, Ca×P product, and UACR as valuable markers for early risk stratification and management of cardiovascular complications in CKD patients. Early identification and timely intervention using these parameters may improve outcomes and guide preventive strategies in CKD progression.

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