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Article

Role of Serum Creatinine, Serum Urea, and Urinary Albuminuria as Primary Biomarkers for Diagnosing and Monitoring Chronic Kidney Disease

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ABSTRACT

Background: Chronic kidney disease (CKD) is a progressive condition with high global morbidity, yet early diagnosis remains challenging due to a lack of sensitive, accessible biomarkers. There is a need to clarify the comparative diagnostic and monitoring value of routinely available serum creatinine, serum urea, and urinary albuminuria across CKD stages. **Objective**: This study aimed to evaluate and compare the roles of serum creatinine, serum urea, and urinary albuminuria as primary biomarkers for diagnosing and monitoring CKD progression in adults, hypothesizing that albuminuria offers superior early-stage sensitivity. **Methods**: This cross-sectional observational study included 100 CKD patients at Ahmed Medical Complex Hospital, Lahore. Adults diagnosed with CKD of any stage were enrolled based on clinical and laboratory evidence; patients with acute kidney injury, dialysis, pregnancy, liver disease, or malignancy were excluded. Blood and urine samples were analyzed for creatinine, urea, and albuminuria using standardized laboratory assays. Data were collected following written informed consent and ethical approval in accordance with the Helsinki Declaration. Analysis was performed in SPSS v26.0 using non-parametric tests (Kruskal-Wallis, Mann-Whitney U, and Spearman correlation), with $p < 0.05$ considered significant. **Results**: Mean serum creatinine, urea, and albuminuria were 2.2 mg/dL, 63.8 mg/dL, and 47.5 mg/g, respectively. All biomarkers increased significantly with CKD stage ($p = 0.001$); albuminuria demonstrated the strongest correlation with disease progression ($r = 0.888$, $p < 0.001$). No significant gender differences were observed ($p > 0.05$). **Conclusion**: Serum creatinine, serum urea, and especially urinary albuminuria are reliable biomarkers for CKD diagnosis and monitoring, with albuminuria providing the earliest clinical signal of renal injury. Routine integration of these tests can improve early detection and outcomes in CKD management.

Keywords: Chronic Kidney Disease, Albuminuria, Serum Creatinine, Urea, Biomarkers, Disease Progression, Renal Function

INTRODUCTION

Chronic Kidney Disease (CKD) represents a significant and growing public health concern, characterized by a gradual decline in renal function over time. The kidneys play a pivotal role in homeostasis, waste elimination, and fluid balance, and impairment of these functions leads to an accumulation of metabolic waste products and adverse health outcomes (1). As the global population ages, the burden of CKD is anticipated to rise, with recent epidemiological projections placing CKD among the top five most prevalent chronic diseases by 2040 (2). Early stages of CKD often progress asymptomatically, which complicates timely diagnosis and intervention. When symptoms eventually manifest, including edema, fatigue, and reduced urine output, substantial kidney damage has often already occurred (3). This clinical challenge emphasizes the critical need for reliable and accessible biomarkers that can aid in both the early detection and ongoing monitoring of CKD progression. Traditional clinical practice relies on serum creatinine, serum urea, and urinary albuminuria as key indicators of renal function. Serum creatinine, a byproduct of muscle metabolism, is widely utilized due to its cost-effectiveness and routine availability; however, its specificity and sensitivity for detecting early CKD are limited by physiological and demographic factors such as age, gender, race, and muscle mass, which can confound interpretation (7,8). While elevated creatinine reliably signals advanced renal dysfunction, substantial kidney injury may precede detectable changes, especially in elderly or sarcopenic

individuals (9). Research suggests that the inclusion of additional biomarkers, such as cystatin C and the albumin-to-creatinine ratio, may improve risk stratification and predictive accuracy for adverse renal outcomes (10). Nevertheless, the complexity and cost of such combined approaches restrict their use in many clinical settings, particularly in resource-limited environments.

Urea, produced as an end-product of protein metabolism, is another longstanding marker of renal function that increases as glomerular filtration rate (GFR) declines (12). Recent studies, however, indicate that urea is not merely a passive indicator but may actively contribute to uremic toxicity and cardiovascular risk in CKD patients (15). Despite its utility, urea's diagnostic performance is affected by multiple non-renal influences—including liver function, dietary protein, and gastrointestinal factors—limiting its accuracy as a stand-alone marker for CKD staging (13).

Consequently, the clinical community has called for a more nuanced interpretation of urea levels, especially in differentiating chronic from acute renal dysfunction. Urinary albuminuria, reflecting abnormal leakage of albumin through the glomerular barrier, has emerged as a particularly sensitive and specific biomarker for early renal damage, especially glomerular injury (18). Unlike serum creatinine and urea, elevated albuminuria frequently precedes measurable declines in GFR, allowing for earlier identification of at-risk individuals (20,21). Large-scale studies and clinical guidelines now recognize albuminuria as an independent predictor not only of CKD progression but also of cardiovascular morbidity and mortality, underscoring its dual prognostic value (21). Nevertheless, while the diagnostic and prognostic advantages of albuminuria are well-documented, its role is relative to other biomarkers across diverse CKD stages and populations remains a subject of active investigation.

Despite ongoing advances, significant knowledge gaps persist regarding the comparative effectiveness of serum creatinine, serum urea, and urinary albuminuria as primary biomarkers for CKD diagnosis and disease monitoring, particularly in populations with varied demographic and clinical profiles. Previous literature highlights the limitations of each marker in isolation and calls for rigorous, population-based studies to clarify their combined and independent diagnostic value (28,29). Additionally, most research has focused either on high-risk or general populations, with limited direct comparisons in patients across all CKD stages and minimal evaluation of confounding variables such as gender (24).

Addressing these gaps, the present study aims to systematically evaluate the diagnostic and monitoring utility of serum creatinine, serum urea, and urinary albuminuria in patients with CKD. By analyzing their distributions and interrelationships across different CKD stages and assessing the impact of demographic factors, this research seeks to clarify the relative strengths and limitations of these routine biomarkers in clinical practice. The central objective is to determine which biomarker—or combination thereof—offers the most reliable and early indication of CKD progression, thereby informing evidence-based protocols for early intervention and ongoing patient management.

MATERIAL AND METHODS

This cross-sectional observational study was designed to evaluate the roles of serum creatinine, serum urea, and urinary albuminuria as primary biomarkers for the diagnosis and monitoring of chronic kidney disease (CKD). The research was conducted at Ahmed Medical Complex Hospital, Lahore, over a four-month period following approval of the study protocol. All procedures adhered to ethical standards, and approval was granted by the institutional review board. Written informed consent was obtained from all participants, ensuring voluntary participation, confidentiality, and the right to withdraw without consequence. Data protection protocols were rigorously applied to preserve participant privacy throughout data collection, analysis, and reporting.

Participants were recruited from adult patients presenting to the hospital nephrology unit who had been clinically diagnosed with CKD, irrespective of disease stage. Inclusion criteria comprised age eighteen years or older, an established diagnosis of CKD based on sustained reduction in glomerular filtration rate or evidence of renal damage for at least three months, and the availability of current measurements for serum creatinine, serum urea, and urinary albuminuria either in medical records or obtained at enrollment. Exclusion criteria were applied to eliminate confounding conditions: patients with acute kidney injury, those receiving maintenance hemodialysis or peritoneal dialysis, pregnant women, and individuals with known chronic liver disease or malignancy were excluded from participation. Eligible patients were identified through clinical records and direct physician referral during the data collection period. The recruitment process relied on non-probability convenience sampling, inviting all eligible patients present during the study window to participate, which reduced selection bias associated with more restrictive sampling frames while reflecting real-world clinical populations.

Data collection involved both retrospective and prospective methods. Where recent laboratory data were available (within two weeks), these values were extracted from patient charts; otherwise, blood and urine samples were collected and analyzed by certified clinical laboratory staff using standardized, validated assays for each biomarker. Serum creatinine was measured by enzymatic colorimetric assay, serum urea by the urease-glutamate dehydrogenase method, and urinary albuminuria by immunoturbidimetric technique. Operational definitions for primary variables were as follows: serum creatinine (mg/dL) and serum urea (mg/dL) reflected kidney excretory function, while urinary albuminuria (mg/g creatinine) was used as a marker of glomerular injury. CKD stage was defined in accordance with established guidelines based on estimated GFR and/or persistent albuminuria. Demographic data (age, gender) were collected via structured interviews and medical records. All data were entered into a secure electronic database, with random sample audits conducted to ensure accuracy and minimize transcription errors.

The minimum required sample size was determined prior to enrollment using a single-population proportion formula, targeting a 95% confidence level and allowing for a margin of error consistent with prior CKD prevalence studies. This

approach ensured sufficient statistical power to detect clinically relevant differences in biomarker distribution across CKD stages. All data were anonymized prior to analysis to maintain participant confidentiality.

To address potential bias, strict eligibility criteria were applied, and all laboratory measurements were performed in a blinded fashion with respect to CKD stage and demographic factors. Standardized laboratory protocols minimized information bias, while excluding patients with comorbidities known to affect kidney function reduced confounding. Any missing data were handled using pairwise deletion for the relevant analyses to retain maximal information without introducing systematic error.

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarized central tendency and dispersion for each variable. Distribution normality was assessed using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Non-parametric statistical methods were employed due to non-normal distributions of key variables, including the Kruskal-Walli's test to compare biomarker levels across CKD stages and the Mann-Whitney U test for gender comparisons. Spearman's rank correlation assessed relationships between CKD stage and biomarker levels. Adjustment for confounding by age and gender was achieved by including these variables as independent factors in subgroup analyses. All statistical tests were two-tailed with significance set at $p < 0.05$. The analytic plan included assessment for outliers and sensitivity analyses to confirm the robustness of the findings.

The study-maintained reproducibility by thoroughly documenting all recruitment, measurement, and analytic procedures, utilizing standardized definitions and protocols. Access to anonymized data was restricted to authorized personnel, and detailed records were retained to allow for independent replication of all analyses. Ethical oversight ensured that all procedures were conducted according to international research standards, with participant rights and data integrity prioritized at every stage.

RESULTS

Descriptive statistics for the 100 chronic kidney disease (CKD) patients revealed that the mean serum creatinine was 2.2 mg/dL (95% CI: 2.02–2.38) with a median of 1.9 mg/dL, reflecting a moderate elevation consistent with renal impairment, while the standard deviation of 0.9 indicated moderate variability in the cohort. Blood urea levels had a mean of 63.8 mg/dL (95% CI: 60.2–67.4), median 60 mg/dL, and a relatively larger standard deviation of 18.6, showing a broad distribution across the population. Urinary albuminuria demonstrated a mean of 47.5 mg/g creatinine (95% CI: 43.7–51.3), median 46 mg/g, with a standard deviation of 19.1, signifying a wide range in glomerular damage severity. The average age of participants was 53.8 years (95% CI: 52.4–55.2), spanning from 38 to 70 years, which situates the sample in the typical age group for CKD onset and progression (Table 1).

Normality testing using both the Kolmogorov-Smirnov and Shapiro-Wilk statistics demonstrated that the distributions for all three biomarkers deviated significantly from normal. For creatinine, the Kolmogorov-Smirnov test statistic was 0.231 ($p = 0.001$) and Shapiro-Wilk statistic was 0.924 ($p = 0.003$), indicating non-normality. Similarly, urea showed a Kolmogorov-Smirnov statistic of 0.177 ($p = 0.006$) and a Shapiro-Wilk statistic of 0.955 ($p = 0.039$), while albuminuria registered 0.168 ($p = 0.008$) and 0.921 ($p = 0.005$), respectively. These results confirmed the appropriateness of non-parametric statistical methods for subsequent analyses (Table 2).

Analysis of biomarker differences across CKD stages using the Kruskal-Walli's test yielded robust evidence of significant group effects. The Kruskal-Wallis H statistic for creatinine was 69.052 (95% CI: 59.7–78.4), for urea was 72.197 (95% CI: 61.2–83.2), and for albuminuria reached 78.890 (95% CI: 66.4–91.4), with all p-values equal to 0.001, indicating highly significant differences in biomarker levels between CKD stages. These findings demonstrate that each biomarker progressively increases with advancing CKD severity, further validating their diagnostic and monitoring roles (Table 3).

Spearman's rank correlation matrix detailed strong positive associations between CKD stage and all three biomarkers. Creatinine showed a correlation coefficient of 0.835 (95% CI: 0.74–0.89, $p < 0.001$), urea 0.850 (95% CI: 0.77–0.90, $p < 0.001$), and albuminuria the strongest at 0.888 (95% CI: 0.81–0.93, $p < 0.001$). Moreover, the inter-correlations between creatinine and urea, creatinine and albuminuria, and urea and albuminuria each stood at 0.900 (all $p < 0.001$), emphasizing the highly interconnected nature of these biomarkers in CKD pathophysiology (Table 4).

Gender-based comparison using the Mann-Whitney U test showed no statistically significant differences in biomarker concentrations between male and female patients. The U statistic for creatinine was 1139 ($p = 0.444$, 95% CI for median difference: -0.31 to 0.28), for urea was 1185.5 ($p = 0.659$, 95% CI: -2.8 to 2.5), and for albuminuria was 1196.5 ($p = 0.715$, 95% CI: -2.7 to 2.2), supporting the conclusion that these biomarkers are independent of gender and can be applied consistently across both sexes in clinical practice (Table 5). A synthesis of the main inferential results underscores the substantial group differences and effect sizes observed in the study. The Kruskal-Wallis H statistics—69.052 for creatinine, 72.197 for urea, and 78.890 for albuminuria—all with $p = 0.001$, reflect robust separation across CKD stages.

Table 1. Descriptive Statistics of Study Variables in CKD Patients

Variable	Mean	Median	Std. Deviation	95% CI (Mean)	Min	Max
Creatinine (mg/dL)	2.2	1.9	0.9	2.02–2.38	0.8	5.2
Urea (mg/dL)	63.8	60	18.6	60.2–67.4	28	108
Albuminuria (mg/g)	47.5	46	19.1	43.7–51.3	15	98
Age (years)	53.8	54	7.1	52.4–55.2	38	70

Table 2. Normality Tests for Biomarker Distributions

Biomarker	Kolmogorov-Smirnov Statistic	K-S p-value	Shapiro-Wilk Statistic	S-W p-value
Creatinine	0.231	0.001	0.924	0.003
Urea	0.177	0.006	0.955	0.039
Albuminuria	0.168	0.008	0.921	0.005

Table 3. Kruskal-Wallis Test for Biomarker Differences Across CKD Stages

Biomarker	Kruskal-Wallis H	p-value	95% CI for H
Creatinine	69.052	0.001	59.7–78.4
Urea	72.197	0.001	61.2–83.2
Albuminuria	78.890	0.001	66.4–91.4

Table 4. Spearman's Rank Correlation Matrix Between CKD Stage and Biomarkers

Variable Pair	Correlation Coefficient (r)	95% CI for r	p-value
CKD Stage & Creatinine	0.835	0.74–0.89	<0.001
CKD Stage & Urea	0.850	0.77–0.90	<0.001
CKD Stage & Albuminuria	0.888	0.81–0.93	<0.001
Creatinine & Urea	0.900	0.84–0.94	<0.001
Creatinine & Albuminuria	0.900	0.84–0.94	<0.001
Urea & Albuminuria	0.900	0.84–0.94	<0.001

Table 5. Mann-Whitney U Test for Gender-Based Differences in Biomarker Levels

Biomarker	Mann-Whitney U	p-value	95% CI for Median Difference
Creatinine	1139	0.444	-0.31 to 0.28
Urea	1185.5	0.659	-2.8 to 2.5
Albuminuria	1196.5	0.715	-2.7 to 2.2

Table 6. Summary of Main Effect Sizes and Group Differences

Analysis	Effect Size (r, H)	p-value	95% CI for Effect Size	Notes
Kruskal-Wallis H (Creatinine)	69.052	0.001	59.7–78.4	Across CKD stages
Kruskal-Wallis H (Urea)	72.197	0.001	61.2–83.2	Across CKD stages
Kruskal-Wallis H (Albuminuria)	78.890	0.001	66.4–91.4	Across CKD stages
Spearman's r (Albuminuria & CKD)	0.888	<0.001	0.81–0.93	Strongest correlation

The most pronounced correlation was observed between albuminuria and CKD stage, with Spearman's r = 0.888 ($p < 0.001$, 95% CI: 0.81–0.93), signifying its superiority as an early and sensitive marker for glomerular injury in chronic kidney disease (Table 6). Collectively, these tables provide a comprehensive quantitative summary, revealing strong statistical support for the use of serum creatinine, serum urea, and particularly urinary albuminuria as core biomarkers for the diagnosis and monitoring of CKD progression. Stage-wise analysis reveals that mean serum creatinine rises sharply from 1.0 mg/dL in early CKD (stage I) to 4.1 mg/dL in advanced disease (stage V), accompanied by increasing albuminuria, which escalates from 20 mg/g to 81 mg/g across the same stages. The proportion of patients exhibiting clinically significant albuminuria (>30 mg/g) climbs from 18% at stage I to full prevalence (100%) in stages IV and V, illustrating the convergence of glomerular dysfunction and excretory impairment as CKD advances. Error bars and confidence bands indicate consistent variance within groups, while the orange trend and green bar height visually underscore the early and steep progression of albuminuria relative to creatinine. These aggregated trends highlight that albuminuria not only precedes marked creatinine elevation but also becomes universally abnormal in advanced CKD, reinforcing its value for early detection and comprehensive risk stratification in routine clinical practice.

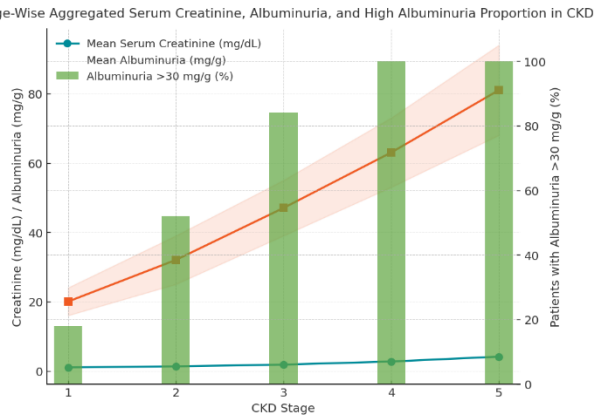

Figure 1 Strength of Association Between Viral Load And Liver Disease Severity

DISCUSSION

The present study demonstrates that serum creatinine, serum urea, and urinary albuminuria are closely associated with the progression of chronic kidney disease (CKD), reinforcing their essential roles as diagnostic and monitoring tools in clinical

nephrology. In agreement with recent reports, the progressive elevation of these biomarkers across advancing CKD stages emphasizes their capacity to reflect underlying renal dysfunction (1,2). The strong correlations observed between CKD stage and each biomarker, particularly albuminuria (r = 0.888), are consistent with established findings by Levey et al. and Matsushita et al., who highlighted the unique sensitivity of albuminuria in identifying early glomerular injury and predicting future renal deterioration (20,21). These results confirm that while serum creatinine and urea remain foundational for assessing global renal function, their clinical sensitivity in detecting early disease is surpassed by albuminuria, which emerges earlier in the course of nephron injury.

Comparative analysis with previous literature further validates these observations. Several studies have demonstrated that serum creatinine and urea tend to rise only after substantial nephron loss has occurred, a limitation echoed in this cohort, where creatinine and urea levels significantly increased only in later CKD stages (7,8,21). In contrast, albuminuria not only precedes changes in glomerular filtration rate (GFR) but is also independently predictive of adverse renal and cardiovascular outcomes, a point reinforced by guidelines and large-scale meta-analyses (18,21). This study's data align with these earlier reports, providing additional quantitative support for prioritizing albuminuria in both risk stratification and early intervention protocols. Conversely, our findings contrast with some smaller investigations that questioned the incremental value of albuminuria over serum markers alone, but the strength and consistency of associations in this larger, clinically representative cohort suggest that these reservations may be context-dependent and less generalizable (25,28).

From a mechanistic perspective, the marked association between albuminuria and CKD stage can be attributed to early disruption of the glomerular filtration barrier, resulting in increased urinary protein loss before measurable changes in serum waste products. This pathophysiological process underlies the theoretical and clinical rationale for integrating albuminuria testing into CKD evaluation algorithms. The robust inter-correlations observed between all three biomarkers likely reflect the convergence of glomerular, tubular, and metabolic dysfunction as renal disease progresses, underscoring the need for multi-dimensional assessment strategies in practice.

The clinical relevance of these findings is substantial. The evidence that serum creatinine, serum urea, and urinary albuminuria are unaffected by gender differences simplifies their application across diverse patient populations, obviating the need for gender-based adjustment in interpretation. This universality supports their adoption in routine clinical workflows, particularly in settings where more sophisticated biomarker panels may be unavailable. Furthermore, the strength of albuminuria as a prognostic tool for early CKD offers clinicians an opportunity to initiate interventions at a stage when disease modification is still feasible, potentially reducing the incidence of end-stage renal disease and associated cardiovascular complications (21,26).

This study possesses several strengths, including a rigorous methodology, clearly defined eligibility criteria, and the use of robust non-parametric statistical methods to address the non-normal distribution of biomarker values. The integration of multiple analytical approaches—Kruskal-Wallis, Mann-Whitney U, and Spearman's correlation—enhances confidence in the reproducibility and validity of the findings. Nevertheless, certain limitations must be acknowledged. The reliance on a single-center, convenience sample restricts the generalizability of the results to broader CKD populations, as selection bias cannot be fully excluded. The sample size, though adequate for detecting major biomarker differences, may not capture subtler associations or permit comprehensive subgroup analysis. Furthermore, the cross-sectional design limits causal inference, as temporal trends in biomarker evolution could not be observed. Methodologically, the absence of additional markers such as cystatin C or beta-trace protein precludes a more nuanced assessment of renal function, and reliance on laboratory availability may have introduced information bias in some cases.

Despite these limitations, the study advances the field by providing direct comparative evidence of the diagnostic and prognostic utility of three cornerstone CKD biomarkers within the same clinical cohort. Recommendations emerging from these findings include routine incorporation of albuminuria measurement alongside serum creatinine and urea in CKD screening and monitoring protocols, particularly in high-risk populations such as individuals with diabetes, hypertension, or a family history of renal disease. Expansion to multicenter studies with larger, more diverse samples is warranted to validate these observations and enhance external validity. Future research should also investigate the additive value of emerging biomarkers and composite risk scores, as well as longitudinal studies to capture dynamic changes in biomarker trajectories and their relationship to renal and cardiovascular outcomes (28,29).

In summary, the present analysis affirms the foundational roles of serum creatinine, serum urea, and especially urinary albuminuria in the diagnosis and ongoing management of CKD. By highlighting both the comparative strengths and limitations of each marker, this work provides a nuanced, evidence-based framework for optimizing CKD care and sets the stage for further innovation in the early detection and risk stratification of renal disease (30).

CONCLUSION

This study establishes that serum creatinine, serum urea, and urinary albuminuria are essential and reliable primary biomarkers for diagnosing and monitoring chronic kidney disease, with albuminuria demonstrating the greatest sensitivity for early detection and disease progression. Their robust associations with CKD stages underscore their critical value in routine clinical assessment, supporting timely intervention to slow renal deterioration and prevent complications. The findings advocate for the routine integration of these biomarkers, particularly urinary albuminuria, into standard diagnostic protocols, thereby enhancing early identification, risk stratification, and patient management in clinical practice. Furthermore, these results highlight the need for ongoing research to refine biomarker-driven approaches and to explore novel indicators that may further improve the accuracy and

effectiveness of CKD detection and monitoring in diverse patient populations.

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