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Original Research Article

Efficacy of Salivary Urea and Creatinine Compared to Serum Levels in Chronic Kidney Disease Patients: A Cross-Sectional Study

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Abstract

Background: Chronic kidney disease (CKD) is a progressive disorder associated with accumulation of metabolic waste products due to declining renal function. Serum urea and creatinine are routinely used for renal assessment; however, repeated blood sampling is invasive and inconvenient. Salivary biomarkers have emerged as potential non-invasive alternatives for evaluating renal dysfunction.

Methods: This hospital-based cross-sectional study included 138 CKD patients attending a tertiary care center. Unstimulated saliva and venous blood samples were collected simultaneously. Serum and salivary urea levels were estimated using the enzymatic urease–GLDH method, while creatinine levels were measured using the modified Jaffe's kinetic method on a fully automated biochemistry analyzer. Correlation analysis and receiver operating characteristic (ROC) curve analysis were performed to evaluate diagnostic efficacy.

Results: The mean serum urea and creatinine levels were 92.4 ± 41.7 mg/dL and 5.48 ± 2.81 mg/dL respectively, while mean salivary urea and creatinine levels were 86.1 ± 38.5 mg/dL and 0.89 ± 0.42 mg/dL respectively. Salivary biomarker levels increased significantly with advancing CKD stages ($p<0.001$). Strong positive correlations were observed between serum and salivary urea ($r=0.884$, $p<0.001$) and serum and salivary creatinine ($r=0.812$, $p<0.001$). Salivary urea demonstrated an AUC of 0.892 with 85.6% sensitivity and 80.4% specificity, while salivary creatinine showed an AUC of 0.851.

Conclusion: Salivary urea and creatinine demonstrated strong correlation with serum biomarkers and significant diagnostic efficacy in CKD patients. Salivary analysis may serve as a reliable, non-invasive, and economical adjunctive tool for screening and monitoring chronic kidney disease.

Keywords: Chronic kidney disease; Salivary urea; Salivary creatinine; Serum creatinine; CKD.

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Introduction

Chronic kidney disease (CKD) is a major global public health problem characterized by progressive and irreversible deterioration of renal function, ultimately leading to end-stage renal disease (ESRD) if not diagnosed and managed early [1]. CKD is associated with significant morbidity, mortality, reduced quality of life, and increased healthcare expenditure. According to the Global Burden of Disease study, CKD affects nearly 10–13% of the world's population and is among the leading causes of death worldwide [1]. The burden is particularly high in developing countries due to the rising prevalence of diabetes mellitus, hypertension, obesity, and aging populations [2]. In India, CKD prevalence has shown a steady increase over the past two decades, with community-based studies estimating prevalence rates ranging from 8–17% [3].

Assessment of renal function primarily relies on measurement of serum biomarkers such as urea and creatinine, along with estimation of glomerular filtration rate (eGFR) [4]. Serum creatinine is widely used as a marker of kidney function because it reflects glomerular filtration; however, blood sample collection is invasive, may cause discomfort, and requires trained personnel and sterile techniques [4]. Similarly, serum urea levels are commonly used to evaluate renal impairment, although they can be influenced by dietary protein intake, hydration status, and catabolic states [5]. Repeated venipuncture for monitoring CKD patients may be inconvenient, especially in pediatric, geriatric, critically ill, or anxious patients

[5]. Saliva has emerged as a promising diagnostic biofluid due to its non-invasive, economical, and easily accessible nature [6]. Saliva contains numerous organic and inorganic constituents that reflect systemic physiological and pathological conditions [6]. Advances in salivary diagnostics have demonstrated the potential utility of saliva in monitoring endocrine disorders, infectious diseases, malignancies, and renal dysfunction [6]. Since urea and creatinine are small molecules capable of diffusing from blood into saliva, their concentrations may increase in parallel with serum levels in patients with impaired renal function [7].

In CKD patients, reduced renal clearance leads to accumulation of nitrogenous waste products in the bloodstream, which subsequently diffuse into salivary secretions [8]. Elevated salivary urea may also contribute to characteristic oral manifestations observed in CKD, including uremic fetor, xerostomia, mucosal irritation, and altered taste sensation [8]. It has been reported significant positive correlations between salivary and serum urea and creatinine levels, suggesting that salivary analysis could serve as an alternative diagnostic approach for assessing renal dysfunction [9,10]. However, variability in study populations, stages of CKD, laboratory methodologies, and sample sizes has resulted in inconsistent findings regarding the diagnostic accuracy and reliability of salivary biomarkers [10].

The use of saliva as a diagnostic tool offers several practical advantages. Saliva collection is simple, painless, non-invasive, and can be performed repeatedly without specialized training or risk of needle-stick injuries and blood-borne infections [11]. This makes salivary diagnostics particularly useful for large-scale screening programs and routine monitoring of CKD patients in resource-limited settings [11]. Furthermore, salivary biomarkers may improve patient compliance and facilitate early detection of renal impairment. Therefore, the present study was aimed to evaluate the levels of salivary urea and creatinine in CKD patients and compare them with corresponding serum levels to determine their diagnostic utility as non-invasive biomarkers of renal dysfunction.

Materials and Methods

Study Design and Setting: This hospital-based cross-sectional observational study was conducted in the Department of Biochemistry in collaboration with the Department of Nephrology at a tertiary care teaching hospital over a period of 12 months. The study was undertaken to evaluate the efficacy of salivary urea and creatinine levels in comparison with serum levels among patients diagnosed with chronic kidney disease (CKD).

Ethical clearance for the study was obtained from the Institutional Ethics Committee prior to commencement of the study, and the study protocol adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment into the study.

Study Population and Sample Size: The study included adult patients previously diagnosed with chronic kidney disease attending the nephrology outpatient department or admitted to the nephrology ward during the study period. Diagnosis and staging of CKD were based on Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which define CKD as abnormalities of kidney structure or function persisting for more than three months, with implications for health.

Patients aged more than 18 years with clinically and biochemically confirmed CKD were included in the study irrespective of gender. Patients with acute kidney injury, salivary gland disorders, oral inflammatory conditions, active oral infections, malignancy, autoimmune diseases affecting salivary secretion, or those receiving radiotherapy to the head and neck region were excluded. Patients unwilling to participate and individuals with conditions known to interfere with saliva production, such as Sjögren syndrome or severe dehydration, were also excluded from the study. A total of 138 participants fulfilling the inclusion criteria were recruited consecutively using a convenient sampling technique.

Clinical Evaluation and Data Collection: Detailed demographic and clinical information of all participants was recorded using a predesigned structured proforma. Data collected included age, gender, duration of CKD, history of diabetes mellitus and hypertension, medication history, dialysis status, and relevant clinical findings.

General physical examination and systemic examination findings were documented. Relevant laboratory investigations including serum urea and serum creatinine values were obtained at the time of sample collection. Estimated glomerular filtration rate (eGFR) was calculated using standard equations and CKD staging was recorded accordingly.

Collection of Saliva Samples: Unstimulated whole saliva samples were collected from all study participants under standardized conditions to minimize variability. Participants were instructed to abstain from eating, drinking, smoking, chewing gum, or performing oral hygiene procedures for at least one hour before sample collection. Saliva collection was performed in the morning hours between 8:00 AM and 10:00 AM to reduce diurnal variation. Participants were asked to rinse their mouth thoroughly with distilled water and rest for

approximately five minutes before sample collection.

Subjects were instructed to sit comfortably in an upright position with the head slightly tilted forward and allow saliva to accumulate naturally in the floor of the mouth without stimulation. Approximately 2–5 mL of unstimulated saliva was collected by passive drooling into sterile disposable containers over a period of 5–10 minutes. The collected samples were immediately transported to the biochemistry laboratory for processing. Saliva samples were centrifuged at 3000 rpm for 10 minutes to remove cellular debris and particulate matter, and the clear supernatant was used for biochemical analysis.

Collection of Blood Samples: Venous blood samples were collected from all participants under aseptic precautions on the same day as saliva collection. Approximately 3–5 mL of venous blood was drawn from the antecubital vein using sterile disposable syringes and transferred into plain vacutainer tubes. The blood samples were allowed to clot and subsequently centrifuged at 3000 rpm for 10 minutes to separate serum. The obtained serum was analyzed for urea and creatinine estimation using standard biochemical methods.

Biochemical Analysis: Serum and salivary urea levels were estimated using the enzymatic urease–glutamate dehydrogenase (GLDH) method, while creatinine levels were measured using the modified Jaffe's kinetic method on a fully automated biochemistry analyzer (Beckman Coulter AU480 Clinical Chemistry Analyzer, Beckman Coulter Inc., Brea, California, USA). All assays were performed according to the manufacturer's instructions using standardized reagents and calibration protocols. Internal quality control measures were maintained throughout the study to ensure accuracy and reliability of biochemical estimations.

Statistical Analysis: The collected data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) software version 25.0 or equivalent statistical software. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparison between serum and salivary biomarker levels among different study groups was performed using the independent sample Student's t-test for two-group comparisons and one-way analysis of variance (ANOVA) for comparison across multiple CKD stages. Correlation between serum and salivary urea and creatinine levels, as well as their association with eGFR, was assessed using Pearson's correlation coefficient after confirmation of normal data distribution using the Shapiro–Wilk test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance, sensitivity, specificity, and area under the curve (AUC) of salivary biomarkers for detection of advanced CKD. A p-value of <0.05 was considered statistically significant.

Results

The present study included 138 patients with chronic kidney disease with a mean age of 52.8 ± 13.6 years. The majority of patients belonged to the 41–60 years age group (51.4%), followed by patients aged >60 years (27.5%) and 18–40 years (21.0%). Male patients predominated the study population constituting 64.5%, while females accounted for 35.5%. Urban residents comprised 58.7% of the study participants. The mean duration of CKD was 4.7 ± 2.9 years. Stage 4 and Stage 5 CKD together accounted for 65.2% of cases, indicating predominance of advanced renal disease. Hypertension was present in 73.9% of patients and diabetes mellitus in 49.3%. Maintenance hemodialysis was being received by 28.3% of the study population. The mean eGFR of the participants was 28.6 ± 16.2 mL/min/1.73m².The mean serum urea level among CKD patients was 92.4 ± 41.7 mg/dL, while the corresponding mean salivary urea level was 86.1 ± 38.5 mg/dL. Similarly, the mean serum creatinine level was 5.48 ± 2.81 mg/dL, whereas the mean salivary creatinine level was 0.89 ± 0.42 mg/dL. Elevated levels of both serum and salivary biomarkers were observed among the study participants, suggesting accumulation of nitrogenous waste products with declining renal function (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Chronic Kidney Disease Patients (n=138)

Variable	Frequency (%)/mean ± SD
Age (years)	52.8 ± 13.6
Age group (years)	
18–40	29 (21.0%)
41–60	71 (51.4%)
>60	38 (27.5%)
Gender	
Male	89 (64.5%)
Female	49 (35.5%)
Residence	

Urban	81 (58.7%)
Rural	57 (41.3%)
Duration of CKD (years)	4.7 ± 2.9
CKD Stage	
Stage 2	11 (8.0%)
Stage 3	37 (26.8%)
Stage 4	44 (31.9%)
Stage 5	46 (33.3%)
Hypertension	102 (73.9%)
Diabetes mellitus	68 (49.3%)
Patients on maintenance hemodialysis	39 (28.3%)
eGFR (mL/min/1.73m²)	28.6 ± 16.2
Parameter	
Serum urea (mg/dL)	92.4 ± 41.7
Salivary urea (mg/dL)	86.1 ± 38.5
Serum creatinine (mg/dL)	5.48 ± 2.81
Salivary creatinine (mg/dL)	0.89 ± 0.42

CKD – Chronic Kidney Disease; eGFR – Estimated Glomerular Filtration Rate

Salivary urea and salivary creatinine levels showed a progressive increase with advancing stages of CKD. Mean salivary urea levels increased from 38.6 ± 10.4 mg/dL in Stage 2 CKD to 126.5 ± 29.4 mg/dL in Stage 5 CKD. Similarly, mean salivary creatinine levels increased from 0.34 ± 0.08 mg/dL in Stage 2 to 1.26 ± 0.31 mg/dL in Stage 5 disease. The differences in salivary biomarker levels across CKD stages were statistically highly significant for both salivary urea and salivary creatinine ($p<0.001$), indicating a strong association between salivary biomarker concentration and severity of renal dysfunction (Table 2).

Table 2: Comparison of Serum and Salivary Urea and Creatinine Levels Among Chronic Kidney Disease Patients

CKD Stage	Salivary Urea (mg/dL)	Salivary Creatinine (mg/dL)
	Mean ± SD	
Stage 2 (n=11)	38.6 ± 10.4	0.34 ± 0.08
Stage 3 (n=37)	59.8 ± 15.7	0.57 ± 0.16
Stage 4 (n=44)	88.3 ± 20.9	0.89 ± 0.25
Stage 5 (n=46)	126.5 ± 29.4	1.26 ± 0.31
p-value	<0.001	<0.001

CKD – Chronic Kidney Disease.

Patients undergoing maintenance hemodialysis demonstrated significantly higher levels of both serum and salivary biomarkers compared to non-dialysis patients. Mean serum urea levels were 132.8 ± 39.5 mg/dL in dialysis patients compared to 76.5 ± 28.7 mg/dL in non-dialysis patients ($p<0.001$). Mean salivary urea levels were also significantly elevated among dialysis patients (121.4 ± 33.8 mg/dL versus 72.1 ± 24.9 mg/dL; $p<0.001$). Similarly, serum creatinine and salivary creatinine levels were significantly higher in dialysis patients than non-dialysis patients (8.42 ± 2.66 vs 4.32 ± 1.71 mg/dL and 1.34 ± 0.29 vs 0.71 ± 0.22 mg/dL respectively; $p<0.001$ for both comparisons) (Table 3).

Table 3: Comparison of Salivary Urea and Salivary Creatinine Levels Across Different Stages of Chronic Kidney Disease

Parameter	Dialysis Patients (n=39)	Non-dialysis Patients (n=99)	p-value
	Mean ± SD		
Serum urea (mg/dL)	132.8 ± 39.5	76.5 ± 28.7	<0.001
Salivary urea (mg/dL)	121.4 ± 33.8	72.1 ± 24.9	<0.001
Serum creatinine (mg/dL)	8.42 ± 2.66	4.32 ± 1.71	<0.001
Salivary creatinine (mg/dL)	1.34 ± 0.29	0.71 ± 0.22	<0.001

CKD – Chronic Kidney Disease

Male patients exhibited slightly higher mean salivary urea and creatinine levels compared to female patients; however, the differences were not statistically significant ($p=0.284$ and $p=0.316$ respectively). CKD patients with diabetes mellitus had significantly higher salivary urea and salivary creatinine levels compared to non-diabetic patients (96.8 ± 40.6 vs 75.5 ± 31.7 mg/dL and 0.99 ± 0.41

vs 0.79 ± 0.36 mg/dL respectively), with statistically significant differences (p=0.012 and p=0.021 respectively). Similarly, hypertensive patients demonstrated significantly elevated salivary biomarker levels compared to normotensive patients, with mean salivary urea levels of 90.9 ± 39.8 mg/dL versus 72.4 ± 28.6 mg/dL (p=0.038) and salivary creatinine levels of 0.93 ± 0.41 mg/dL versus 0.76 ± 0.34 mg/dL (p=0.044) (Table 4).

Table 4: Comparison of Serum and Salivary Biomarker Levels Between Dialysis and Non-dialysis Chronic Kidney Disease Patients

Variable	Salivary Urea (mg/dL) Mean ± SD	p-value	Salivary Creatinine (mg/dL) Mean ± SD	p-value
Gender				
Male	88.4 ± 39.1	0.284	0.92 ± 0.43	0.316
Female	81.9 ± 36.8		0.84 ± 0.39	
Diabetes Mellitus				
Present	96.8 ± 40.6	0.012	0.99 ± 0.41	0.021
Absent	75.5 ± 31.7		0.79 ± 0.36	
Hypertension				
Present	90.9 ± 39.8	0.038	0.93 ± 0.41	0.044
Absent	72.4 ± 28.6		0.76 ± 0.34	

A strong positive correlation was observed between serum and salivary urea levels (r=0.884, p<0.001) as well as between serum and salivary creatinine levels (r=0.812, p<0.001). Salivary urea and salivary creatinine levels also demonstrated significant negative correlations with eGFR (r=-0.768 and r=-0.703 respectively; p<0.001), indicating increasing salivary biomarker concentrations with worsening renal function (Table 5).

Table 5: Association of Salivary Urea and Salivary Creatinine Levels with Clinical Variables Among Chronic Kidney Disease Patients

Parameters Compared	Correlation Coefficient (r)	p-value
Serum urea vs Salivary urea	0.884	<0.001
Serum creatinine vs Salivary creatinine	0.812	<0.001
Salivary urea vs eGFR	-0.768	<0.001
Salivary creatinine vs eGFR	-0.703	<0.001

eGFR – Estimated Glomerular Filtration Rate

Receiver operating characteristic analysis demonstrated excellent diagnostic performance of salivary biomarkers for detection of advanced CKD. Salivary urea at a cut-off value of >79 mg/dL showed 85.6% sensitivity and 80.4% specificity with an AUC of 0.892 (95% CI: 0.836–0.948; p<0.001). Salivary creatinine at a cut-off value of >0.76 mg/dL demonstrated 81.1% sensitivity and 76.1% specificity with an AUC of 0.851 (95% CI: 0.788–0.915; p<0.001) (Table 6).

Table 6: Correlation and Diagnostic Performance of Salivary Biomarkers in Chronic Kidney Disease Patients

Biomarker	Salivary urea	Salivary creatinine
Cut-off Value	>79 mg/Dl	>0.76 mg/dL
Sensitivity (%)	85.6	81.1
Specificity (%)	80.4	76.1
AUC (95% CI)	0.892 (0.836–0.948)	0.851 (0.788–0.915)
p-value	<0.001	<0.001

AUC – Area Under Curve; CI – Confidence Interval; r – Correlation coefficient.

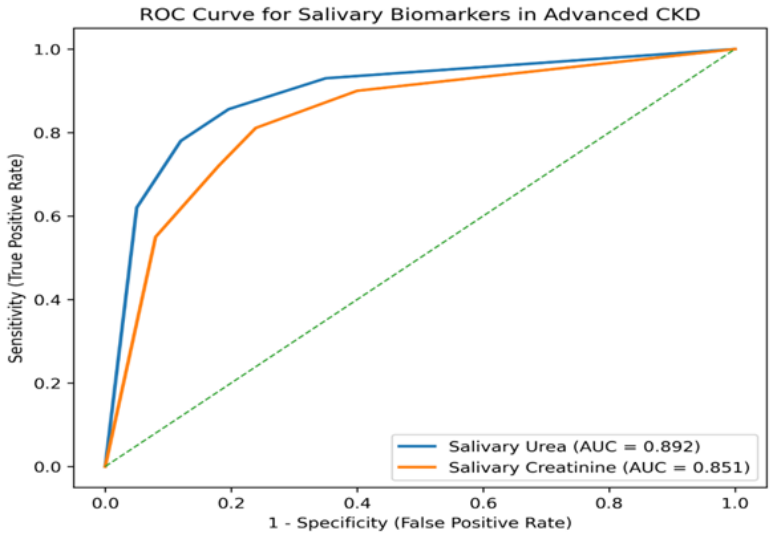

Figure 1: Receiver Operating Characteristic (ROC) Curve Analysis of Salivary Urea and Salivary Creatinine for Detection of Advanced Chronic Kidney Disease

Discussion

The present cross-sectional study evaluated the efficacy of salivary urea and creatinine as non-invasive biomarkers in patients with chronic kidney disease (CKD) and demonstrated significant correlations between salivary and serum biochemical parameters. The study population had a mean age of 52.8 ± 13.6 years, with the majority belonging to the 41–60 years age group and a predominance of males (64.5%). Similar demographic trends have been reported in previous CKD studies by Deng et al., and Wang et al., where middle-aged males constitute the majority of CKD patients due to higher prevalence of diabetes, hypertension, smoking, and cardiovascular risk factors [12,13]. The high prevalence of hypertension (73.9%) and diabetes mellitus (49.3%) observed in the present study is consistent with established evidence identifying these conditions as the leading causes of CKD worldwide Hustrini et al., and Erfanpoor et al., [14,15].

In the present study, elevated serum urea (92.4 ± 41.7 mg/dL) and serum creatinine levels (5.48 ± 2.81 mg/dL) were associated with correspondingly high salivary urea (86.1 ± 38.5 mg/dL) and salivary creatinine levels (0.89 ± 0.42 mg/dL). These findings suggest that salivary concentrations of nitrogenous waste products increase in parallel with serum concentrations in CKD patients [16]. The physiological explanation for this observation lies in progressive nephron loss and impaired glomerular filtration, resulting in accumulation of urea and creatinine in blood, which subsequently diffuse into saliva through semipermeable salivary gland membranes [17]. Similar findings have been reported by Nagarathinamet al., and Chacko et al., who demonstrated significantly elevated salivary urea and creatinine levels among CKD patients compared to healthy controls [18,19].

A significant finding of the present study was the progressive increase in salivary biomarker levels with advancing CKD stage. Mean salivary urea increased from 38.6 ± 10.4 mg/dL in Stage 2 CKD to 126.5 ± 29.4 mg/dL in Stage 5 CKD, while salivary creatinine increased from 0.34 ± 0.08 mg/dL to 1.26 ± 0.31 mg/dL ($p<0.001$). These findings indicate that salivary biomarker concentrations reflect disease severity and worsening renal function. Similar stage-wise increases in salivary renal biomarkers have been reported by Vacarel et al., and SaiKiran et al., [20,21]. The increase in salivary biomarker levels with CKD progression may be attributed to declining glomerular filtration rate, impaired renal clearance, and increased permeability of salivary gland membranes secondary to uremic changes and microvascular alterations associated with chronic renal dysfunction [22].

The comparison between dialysis and non-dialysis patients further strengthened the diagnostic utility of salivary biomarkers. Dialysis patients showed significantly higher salivary urea (121.4 ± 33.8 mg/dL) and salivary creatinine levels (1.34 ± 0.29 mg/dL) compared to non-dialysis patients (72.1 ± 24.9 mg/dL and 0.71 ± 0.22 mg/dL respectively; $p<0.001$). These findings are consistent with studies by Poposki et al., and Abu Raihan et al., who observed markedly elevated salivary biomarker levels among hemodialysis patients [23,24]. This may be explained by severe renal impairment and accumulation of metabolic toxins between dialysis sessions, resulting in greater diffusion of nitrogenous compounds into saliva [24]. The present study also demonstrated significantly higher salivary biomarker levels

among diabetic and hypertensive CKD patients. Diabetic patients showed significantly elevated salivary urea and creatinine levels compared to non-diabetics ($p=0.012$ and $p=0.021$ respectively), while hypertensive patients also demonstrated significantly increased levels ($p<0.05$). Similar findings have been reported in previous studies by Rodrigues et al., and Liyanage et al., evaluating salivary biomarkers in diabetic nephropathy [25,26]. Chronic hyperglycemia and hypertension accelerate glomerular damage, endothelial dysfunction, and nephron loss, thereby worsening renal impairment and increasing retention of metabolic waste products [26].

One of the most clinically relevant findings of the present study was the strong positive correlation between serum and salivary biomarkers. Salivary urea showed a very strong positive correlation with serum urea ($r=0.884$, $p<0.001$), while salivary creatinine correlated strongly with serum creatinine ($r=0.812$, $p<0.001$). Additionally, both salivary biomarkers showed significant negative correlations with eGFR, indicating increasing salivary levels with declining renal function. Similar strong correlations have been reported by Renda et al., and Tahir et al., [27,28]. Among the two biomarkers, salivary urea demonstrated slightly superior correlation and diagnostic performance, likely because urea diffuses more readily across salivary gland membranes owing to its lower molecular weight [28].

Receiver operating characteristic analysis demonstrated excellent diagnostic efficacy of salivary biomarkers for detecting advanced CKD. Salivary urea showed an AUC of 0.892 with 85.6% sensitivity and 80.4% specificity, while salivary creatinine demonstrated an AUC of 0.851 with 81.1% sensitivity and 76.1% specificity. These findings indicate high discriminatory ability of salivary biomarkers for identifying advanced renal dysfunction [29,30]. The high diagnostic accuracy observed in the present study suggests that salivary analysis may serve as a reliable, non-invasive alternative for CKD screening and monitoring, particularly in patients requiring repeated biochemical evaluation or in resource-limited settings where blood collection may be challenging.

Limitations

The present study was conducted at a single tertiary care center with a relatively limited sample size, which may affect the generalizability of the findings. Healthy controls were not included for comparison. Variations in salivary flow rate, hydration status, dietary intake, and oral health conditions could have influenced salivary biomarker concentrations. Additionally, longitudinal follow-up was not performed to assess temporal changes in salivary biomarkers with disease progression or treatment.

Conclusion

The present study demonstrated a strong positive correlation between salivary and serum urea and creatinine levels in chronic kidney disease patients. Salivary biomarker levels increased significantly with advancing CKD stages and were markedly elevated among dialysis patients, indicating their close association with renal dysfunction severity. Salivary urea showed particularly high diagnostic accuracy with excellent sensitivity and specificity for detecting advanced CKD. As saliva collection is non-invasive, simple, economical, and easily repeatable, salivary urea and creatinine may serve as reliable adjunctive biomarkers for screening and monitoring CKD, especially in settings where repeated venipuncture is difficult or resource availability is limited.

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