Comparison of associations of Urine Protein-Creatinine ratio versus Albumin-Creatinine ratio with Diabetes Mellitus, Hypertension and Kidney Disease

Ajay Kumar[1], Mukul Sharma[2], Bhasker Mukherjee[3], Lekha Sharma[4]

[1]Department of Biochemistry, PIMS, Udaipur, Rajasthan, India

[2,4]Department of Biochemistry, PMCH, Udaipur, Rajasthan, India

[3]Department of Biochemistry, AFMC, Pune, Maharashtra, India

Abstract

Background: Either protein-to-creatinine ratio (PCR) or albumin-to-creatinine ratio (ACR)can be accepted for estimation of proteinuria in patients with chronic kidney disease (CKD). Proteinuria is associated with an increased risk of progressive kidney and cardiovascular disease and is used to monitor the progress of kidney diseases or response to therapy. Only a few studies have directly compared the performance of these two measures with regard to associations with clinical outcomes, and they were not in concordance.

Aim and objectives of the study: The aim of this study was to examine the correlation between PCR and ACR and compare the diagnostic performance of PCR and ACR in chronic kidney diseases, diabetes mellitus (DM), hypertension (HTN) and Diabetes mellitus with hypertension (DM+HTN) and HTN to investigate the optimal test to identify significant proteinuria.

Material & methods: A Cross-sectional study was undertaken. Urine samples were obtained from 203 patients with CKD, DM and HTN who visited tertiary health care center from Sep 2022 to May 2023. PCR and ACR are measured from a random spot urine sample.

Results: There was a strong positive correlation between the PCR and ACR. A ROC curve analysis for

PCR, considering ACR as the gold standard for CKD, DM, HTN, & DM+HTN, showed sensitivity and specificity of 93.33%, 100%, 90%, 93.33 and 96.67%, 96.67%, 96.67%, 100% respectively. The subgroup analysis of various disease groups had a significant association with ACR & PCR.

Conclusion: Both PCR and ACR are significant in the evaluation of risk stratification for CKD, diabetic and non-diabetic nephropathy.

Keywords: Chronic kidney disease (CKD), protein-to-creatinine ratio (PCR), albumin-to-creatinine ratio (ACR) diabetes mellitus (DM), hypertension (HTN)

Introduction

Globally, in 2017, 1·2 million (95% uncertainty interval [UI] 1·2 to 1·3) people died from CKD. The global all-age mortality rate from CKD increased 41·5% (95% UI 35·2 to 46·5) between 1990 and 2017, although there was no significant change in the age-standardised mortality rate (2·8%, −1·5 to 6·3). In 2017, 697·5 million (95% UI 649·2 to 752·0) cases of all-stage CKD were recorded, for a global prevalence of 9·1% (8·5 to 9·8). The global all-age prevalence of CKD increased 29·3% (95% UI 26·4 to 32·6) since 1990, whereas the age-standardized prevalence remained stable (1·2%, −1·1 to 3·5). CKD resulted in 35·8 million (95% UI 33·7 to 38·0) DALYs in 2017, with diabetic nephropathy accounting for almost a third of DALYs, where the increased burden of CKD due to diabetes mellitus (DM) and to a lesser extent due to hypertension (HTN) and other causes outpaced the burden expected by demographic expansion[1].

The identification and quantification of proteinuria are central elements in the diagnosis and management of chronic kidney disease (CKD). Proteinuria has an association with an increased risk of progressive kidney failure[2], cardiovascular disease, and mortality[3],

Address for Correspondence:

Dr. Mukul Sharma

Assistant Professor, Department of Biochemistry

PMCH, Udaipur, Rajasthan, India

Email: mklsharma20@gmail.com

and it is commonly used to monitor the progress of kidney disease or the effectiveness of therapy[4].

The etiology of CKD varies considerably throughout India. Parts of the states of Andhra Pradesh, Odisha, and Goa have high levels of CKD of unknown etiology (CKDu), which is chronic interstitial nephropathy with insidious onset and slow progression[5].

The same microalbuminuria has significance as an early sign of progressive cardiovascular and renal disease in individuals with certain conditions, such as HTN and DM[6].

Added to other causes is the growing burden of HTN and DM. By 2030, India is expected to have the world's largest population of patients with diabetes[2].

Some studies mentioned that albumin to creatinine ratio (ACR) is preferred as a marker over the total urine protein to creatinine ratio (PCR), the cost of measuring albumin may become restricted in its use in developing countries[7].

Increased total proteinuria and albuminuria are independently associated with adverse outcomes in individuals with CKD, with and without other conditions like diabetes mellitus[8].

Regardless of the enormous studies in literature proving their predictive and prognostic potential, there have been very few studies of head-to-head comparisons of albuminuria versus total proteinuria and there have been discrepancies in which measure is used in research studies and day-to-day clinical practice. Some studies have found albuminuria to be more significant than proteinuria[9], others have shown vice versa that total proteinuria is significant[10].While still, others have found both measures to have equally predictive values for outcomes such as end-stage renal disease (ESRD) and mortality[11].

In addition to the above facts, some studies show that ACR and PCR are significantly correlated among CKD and non-CKD populations [12], others have not in concordance[3].

Aim & Objectives: The aim of this study was to investigate the correlation between PCR and ACR in patients with CKD, DM, DM with HTN and HTN. The further objective of study was to compare the diagnostic performance of PCR and ACR in CKD, DM, DM with HTN and HTN.

Material & Methods:

This was a cross-sectional study to analyze a group of patients, diagnosed cases with CKD, DM, DM with HTN, and HTN from September 2022 to May 2023. Early morning first voided urine samples were obtained from 203 patients who visited OPD and IPD in the tertiary health care center at Udaipur, Rajasthan. The age group of subjects studied lies in the range of 30-65 years. As per a previous study pooled prevalence of CKD was 14%[13]. To calculate the sample size for the study, the formula used with the precision of 05% and 95% confidence level minimum sample size required 193 cases. Known cases with DM, HTN & CKD were considered as inclusion criteria, whereas patients diagnosed with AKI, UTI, pregnancy & malignancies were excluded from the study. Forty healthy individuals were recruited as controls.

Early morning first voided urine sample was collected in a sterilized urine container. Urine albumin concentration was estimated by the Particle-enhanced turbidimetric inhibition immunoassay method by using Cobas C311 (Roche) automated biochemistry analyser. Urine Total protein concentration was determined by Pyrogallol red (Dye) binding method. Urine Creatinine concentration was estimated by the modified kinetic Jaffe method. The sample collection started after the clearance from Institutional Ethical Committee (PMU/PMCH/IEC/2022/59).

Diagnostic cut-off for ACR: Normoalbuminuria- < 30 mg/g (3 mg/mmol), **Microalbuminuria**- 30–300 mg/g (3–30 mg/mmol), **Macroalbuminuria**- > 300 mg/g (30 mg/mmol)

Diagnostic cut-off for PCR: Normal- <0.13 protein in mg/dL, **Proteinuria-** ≥0.13 protein in mg/dL

Statistical interpretations:

All information was fed into a MS Excel sheet and analyzed by SPSS 20.0statistics software. The correlation between PCR and ACR was determined by the Pearson method. ROC curve analysis for PCR, considering ACR as the gold standard for diagnosis (CKD, DM, HTN and DM with HTN). Sub-group analysis for the ACR and PCR with various disease groups was performed by ANOVA.

Results:

Table 1: Characteristics of Patient and Control

Patient		Control	
Characteristics	**203 patients**	**Characteristics**	**40 Controls**
Mean±SD Age (Range in years)	48.65 ±17 (Range=12-85)	**Mean Age±SD (years)**	33.96 ±13 (Range=12-60)
Male (%)	135 (66.5)	**Male (%)**	22 (55)
Female (%)	68 (33.5)	**Female (%)**	18 (45)
Diagnosis:		**ACR (Median & Range)**	9.78 (3.15-57)
Normotensive DM (%)	54 (26.6)	**PCR (Median & Range)**	0.070 (0.22-0.93)
HTN (%)	51 (25.1)		
DM & HTN (%)	17 (8.3)		
CKD (%)	81 (39.9)		
ACR (Median & Range)	79.18 (1.02-2266)		
PCR (Median & Range)	0.332 (0.005-569)		

Table 1 shows that population of males were two-fold than females in patient as well as control group.

The demographic and clinical characteristics of patient and control group were mentioned in table 1. In our study population number of males were two folded than females in patient as well as control group. The mean age of patient and control group were 48.65 ± 17.0years and 33.96 ± 13 years respectively.

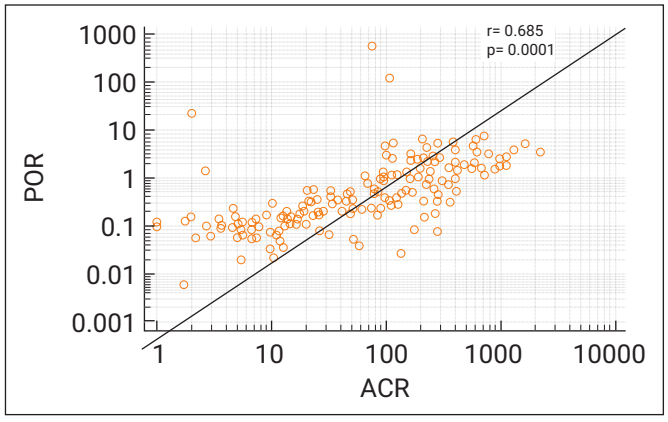
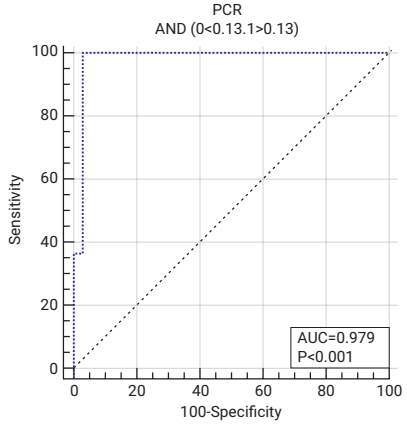


Figure 1: Shows a strong positive correlation between PCR & ACR.

The figure 1 shows association of the PCR and ACR. There was a strong positive correlation between the PCR and ACR (r =0.685, p= 0.0001).

DM ROC

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>0.1259	100.00	88.4-100.0	96.67	82.8 - 99.9	30.0	0.00



HTN ROC

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>0.1259	90.00	73.5-97.9	96.67	82.8-99.9	27.00	0.10

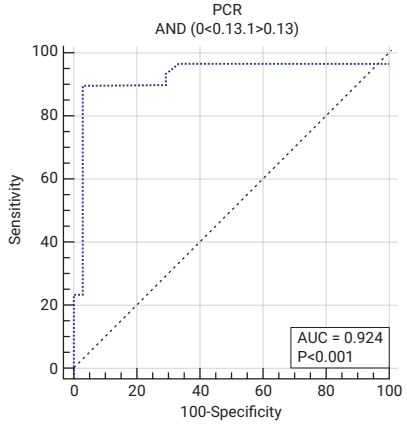
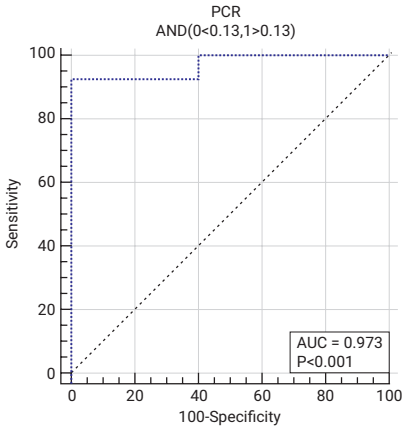


Figure 2: Shows a ROC curve analysis for PCR, considering ACR as gold standard for DM & HTN.

DM & HTN ROC

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>0.1033	93.33	68.1-99.8	100.00	78.2-100.0	28.00	0.067



CKD ROC

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>0.1259	93.33	77.9-99.2	96.67	82.8 - 99.9	28.00	0.069

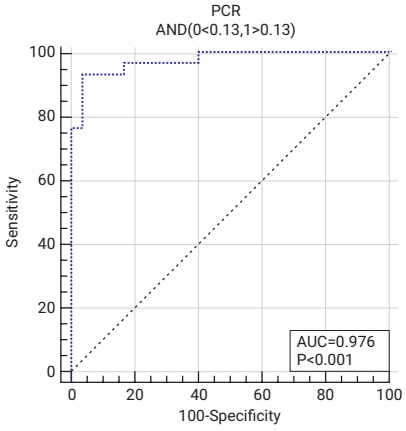


Figure 3: A ROC curve analysis for PCR, considering ACR as gold standard for CKD and DM with HTN.

A ROC curve analysis for PCR, considering ACR as the gold standard for CKD, DM, HTN & DM with HTN, showed sensitivity and specificity of 93.33%, 100%, 90%, 93.33 and 96.67%, 96.67%, 96.67%, 100% (p<0.001) respectively **(Fig 2 and 3).** The subgroup analysis of various disease groups had a significant association (α<0.05) with ACR & PCR.

Table 2: Subgroup Analysis by one-way ANOVA

ACR				
Factor	**n**	**Mean**	**SD**	**Different (P<0.05) from factor nr**
DM (1)	54	116.54	255.54	(3)
DM & HTN (2)	17	261.23	218.60	
HTN (3)	51	400.67	439.77	(1)(4)
KD (4)	81	94.91	132.50	(3)
*The subgroup analysis by one-way ANOVA, which revealed a statistically significant difference among means of the different disease groups for ACR.				

Table 2 demonstrates the subgroup analysis for ACR by one-way ANOVA, which revealed a statistically significant difference among means of the different disease groups.

Table 3: Subgroup Analysis by one-way ANOVA

PCR				
Factor	**n**	**Mean**	**SD**	**Different (P<0.05) from factor nr**
DM (1)	54	0.49	0.95	(2)
DM & HTN (2)	17	34.52	137.79	(1)(3)(4)
HTN (3)	51	4.36	15.51	(2)
KD (4)	81	0.67	1.22	(2)
*The subgroup analysis by one-way ANOVA, which revealed a statistically significant difference among means of the different disease groups for PCR.				

Table 3 demonstrates the subgroup analysis for PCR by one-way ANOVA, which revealed a statistically significant difference among means of the different disease groups.

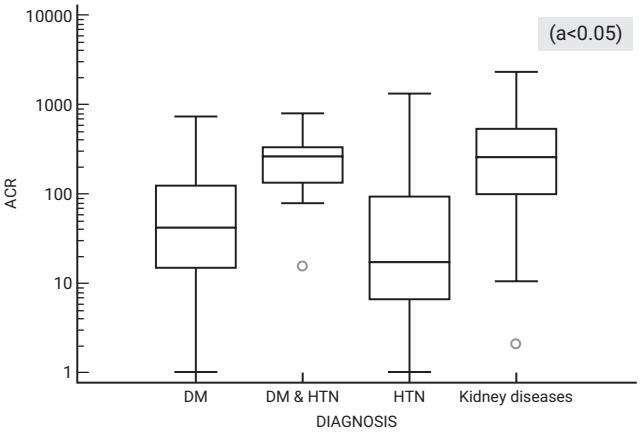


Figure 4: Shows Tukey-Kramer Post hoc test for all pairwise comparisons with ACR.

The Figure 4 displays Tukey-Kramer post hoc test for all pairwise comparisons of various disease groups with ACR, which revealed a statistically significant difference among means of the different disease groups.

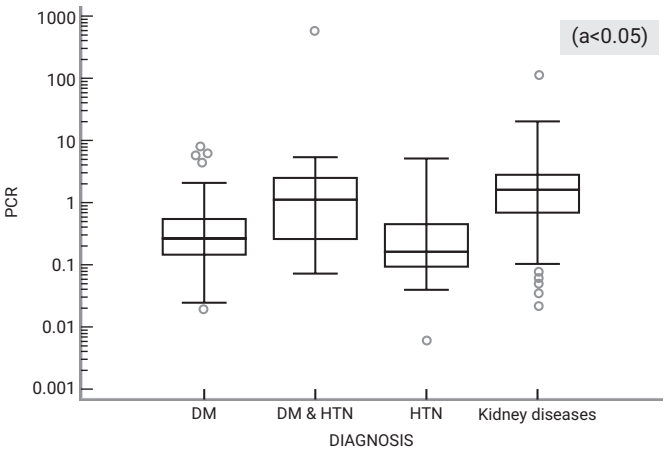


Figure 5: Shows Tukey-Kramer Post hoc test for all pairwise comparisons with PCR.

The Figure 5 displays Tukey-Kramer post hoc test for all pairwise comparisons of various disease groups with PCR, which revealed a statistically significant difference among means of the different disease groups.

Discussion:

Estimation of albuminuria and total proteinuria is a vital aspect of the management and prognosis of patients with CKD. However, there is uncertainty regarding the best measure of urinary protein excretion-this has clinically imperative implications from a practical and cost-effectiveness perception[12]. The same microalbuminuria is significant as an early sign of progressive cardiovascular disease and renal disease in individuals with certain lifestyle disorders, such as HTN and DM[6].Diabetic nephropathy, which is accountable for about 20% of cases of chronic renal failure, is the most common causative factor of end-stage renal failure [14,15].

In this study, a significant positive correlation between the PCR and ACR was observed which was similar to the previous study by Fisher et al[12]. We found that the associations with ACR and PCR were seen in all groups of patients (CKD, DM, DM with HTN and HTN).

In a previous study, Kim et al reported that ACR and PCR did not correlate well at lower ranges of proteinuria[16]. In divergence, another study by Methven et al reported that when proteinuria was measured <0.5 g/d and <1.0 g/d, PCR was more sensitive as compared with ACR as a screening test[17]. Coherent with our findings, several other studies among CKD and non-CKD patients have shown strong correlations between ACR and PCR[18,19].

The subgroup analysis by one-way ANOVA, revealed a statistically significant difference among means of the different disease groups. This difference in means of various groups of this study suggests that ACR and PCR are altered according to pathophysiological changes in the kidney in different stages of disease and comorbidities. Therefore, Proteinuria (PCR) and albuminuria (ACR) are markers for kidney disease in evidently healthy subjects as well as in patients with different comorbidities such as diabetes mellitus, hypertension, or obesity [12,20].

We analyzed that collection of 24h urine samples and reagent strip devices are not enough to measure protein loss and proteinuria detection. Here is an alternative view to detect even low levels of protein loss in chronic kidney disease (CKD) which is a little more expensive, more accurate, and reliable test for proteinuria. As a result of early or timely detection, it becomes imperative.

We also found that, in ROC curve analysis for PCR and ACR, ACR is the gold standard for CKD, DM, HTN & DM WITH HTN. It is also more sensitive & specific in its working. The other group also had a significant correlation with ACR & PCR. Therefore, PCR as well as ACR are significant in the evaluation for CKD, diabetic and non-diabetic nephropathy as well as monitoring of response to treatment. However, Albuminuria is the earliest marker of glomerular diseases, including diabetic glomerulosclerosis, where it generally appears before the low glomerular filtration rate (GFR). Albumin is the predominant protein in the vast majority of proteinuria kidney diseases. Because total protein assays are insensitive at low concentrations relatively large increases in urine albumin loss (doubling) can occur without causing a measurable increase in urinary total protein[21]. Albumin immunoassay, having high sensitivity for detecting increased protein loss, proves that ACR is superior. But laboratory diagnostics do not stand still: increasing evidence suggests that albumin measurement is both a technically superior test and a better marker for kidney damage[22].

ACR should replace PCR as the test of choice for proteinuria detection, not based solely upon their relative abilities to estimate total protein loss, but on factors including that albumin measurement can be standardized and is more precise at lower levels of proteinuria, that it is already the test of choice in people with diabetes, and that it is the predominant protein in the vast majority of proteinuria kidney diseases[23].

Urinary albumin measurement provides a more specific and sensitive measure of changes in glomerular permeability than total protein.

Conclusion:

There is a significant relationship between Urine Protein-Creatinine Ratio versus Albumin-Creatinine Ratio. Both PCR and ACR are significant in the evaluation of risk stratification for CKD, diabetic and non-diabetic nephropathy as well as monitoring of

response to treatment. Early identification of patients with significant proteinuria will prompt early referral and initiation of renal protective therapy.

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