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**Original Paper**

# Evaluation of Urinary Indices for Albuminuria and Proteinuria in Patients with Chronic Kidney Disease

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**Key Words**
Albuminuria • Albumin-to-creatinine ratio • Albumin-to-protein ratio • Proteinuria • Protein-to-creatinine ratio • Urine protein electrophoresis

**Abstract**
***Background/Aims:*** Either protein-to-creatinine ratio (PCR) or albumin-to-creatinine ratio (ACR) can be adopted for estimation of proteinuria in patients with chronic kidney disease (CKD). Estimated protein excretion rate (ePER) and estimated albumin excretion rate (eAER) may be superior to ACR and PCR. Reports show that urine albumin-to-protein ratio (APR) may be useful in detecting tubular proteinuria, but should be compared with urine protein electrophoresis (PEP). ***Methods:*** Both 24-h urine and spot urine were collected from 77 stable CKD patients for measurement of albumin, protein, and creatinine, and PEP. Based on MDRD and CKD-EPI equations, $ePER_{MDRD}$, $ePER_{CKD-EPI}$, $eAER_{MDRD}$ and $eAER_{CKD-EPI}$ were calculated to estimate daily proteinuria and albuminuria. Glomerular CKD was defined by clinical and/or pathological evidence. ***Results:*** ACR correlated significantly with PCR. However, microalbuminuria was present in patients without pathologic proteinuria. Twenty-four-hour urine albumin correlated better with $eAER_{MDRD}$ and $eAER_{CKD-EPI}$ than ACR, and 24-h urine protein correlated better with $ePER_{MDRD}$ and $ePER_{CKD-EPI}$ than PCR. APR significantly but not well correlated with the albumin fraction in urine PEP. The albumin fraction obtained from urine PEP was significantly higher in patients with glomerulopathy than those with non-glomerular CKD, whereas there were no differences in APR between groups. In contrast with APR, the albumin fraction in urine PEP was independently associated with glomerular CKD. ***Conclusions:*** Both PCR and ACR are useful in evaluation of proteinuria. In quantifying daily proteinuria and albuminuria, ePER and eAER are superior to PCR and ACR, respectively. Compared with APR, urine PEP is more useful in diagnosing glomerular proteinuria.



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## Introduction

Because proteinuria is an important marker of renal risk in both the general population and patients with chronic kidney disease (CKD) [1], accurate identification and quantification of proteinuria are essential for the detection, diagnosis and management of CKD. Although 24-h urine proteinuria is a gold standard for quantitative measurement, protein-to-creatinine ratio (PCR) from spot urine is a reasonable alternative [2]. Traditionally, total protein in urine has been measured using chemical methods such as turbidimetry. Because PCR is a measure of protein excretion rate (PER) per unit of muscle mass, consideration of urine creatinine excretion rate (CER) would improve the correlation between PCR and 24-h urine proteinuria [3].

Previously, urine albumin was measured to determine whether a diabetic patient had incipient nephropathy, as an albumin excretion rate (AER) ≥ 30 mg/d generally reflects an alteration in the structure of the glomerular capillary wall [4]. Recent guidelines recommend measuring albuminuria in all CKD patients based on the prognostic importance of albuminuria for kidney disease outcomes, as well as for cardiovascular disease and mortality [5-7]. Although 24-h urine albuminuria is the gold standard for quantitative measurement, the preferred method for assessing albuminuria in both diabetic and non-diabetic patients is urine albumin-to-creatinine ratio (ACR) measurement in a first-void spot urine specimen [8, 9]. Considering the cost required for immunoassays of albuminuria, however, whether testing for both albuminuria and proteinuria is necessary among CKD patients remains unclear. Similar to PER, urine albumin excretion rate (AER) can be estimated from ACR, reflecting the influence of creatinine excretion [10].

Qualitative analysis of proteinuria is another important aspect when assessing proteinuric CKD patients. Urine protein electrophoresis (PEP) has been useful for this purpose, and the urine albumin-to-protein ratio (APR) derived from ACR/PCR was proposed as a new tool for differentiation of tubular proteinuria [11]. Although APR can be obtained easily and is inexpensive compared with PEP, determining its value for differentiation between glomerular and tubular proteinuria requires further investigation.

This study was undertaken to address these issues of quantitative and qualitative evaluation of proteinuria in CKD patients. First, we compared detection between proteinuria and albuminuria in the same 24-h urine and spot urine samples. Second, estimated protein excretion rate (ePER) and estimated albumin excretion rate (eAER) were calculated using estimated creatinine excretion rate (eCER) [12] to examine if their correlations with 24-h urine proteinuria and albuminuria are improved, respectively, along the wide range of proteinuria. Third, urine APR was compared with urine PEP to test which was superior for the diagnosis of glomerulopathy in CKD patients.

## Patients and Methods

*Patients*

We collected 24-h and spot urine samples from 77 patients who were admitted to our hospital and diagnosed with CKD [5]. Patients with acute kidney injury, any infection, and malignancies were excluded. We classified patients into those with glomerular and non-glomerular CKD based on clinical and/or pathological evidence. Clinically, glomerulopathy was diagnosed when overt proteinuria (≥ 500 mg/d) was accompanied by hematuria. On the other hand, we counted overt $\beta_2$-microglubulinuria as representing tubulointerstitial disease.

Spot urine was obtained in the morning immediately after finishing 24-h urine collection. Adequacy of 24-h urine collection was confirmed by appropriate ranges of urinary creatinine excretion. In adults under the age of 50 years, daily creatinine excretion should be 20 to 25 mg/kg of lean body weight in men and 15 to 20 mg/kg of lean body weight in women. From the ages of 50 to 90 years, there is a progressive decline in creatinine excretion (to about 10 mg/kg in men, lower in women) due primarily to decreased muscle mass [13].

*Measurements*

Urine albumin concentration was determined by turbidimetric immunoassay using Autokit Micro Albumin (Wako Diagnostics, Mountain View, CA, USA), and urine protein concentration was measured with a pyrogallol red-molybdate complex in an automated analyzer [14]. Urine creatinine concentration was determined using the kinetic rate Jaffe method. ACR was calculated as spot urine albumin concentration divided by spot urine creatinine concentration, and PCR was calculated as spot urine total protein concentration divided by spot urine creatinine concentration.

Daily albuminuria and proteinuria were measured from 24-h urine collection, and estimated albumin excretion rate (eAER) and estimated protein excretion rate (ePER) were calculated from ACR and PCR, respectively, by multiplying estimated creatinine excretion rate (eCER) [10, 15]. $eCER_{MDRD}$ and $eCER_{CKD\text{-}EPI}$ were derived from MDRD and CKD-EPI equation, and $eAER_{MDRD}$, $eAER_{CKD\text{-}EPI}$, $ePER_{MDRD}$, and $ePER_{CKD\text{-}EPI}$ were calculated to estimate daily proteinuria and albuminuria [12].

$$eAER_{MDRD} = ACR \times eCER_{MDRD}$$
$$eAER_{CKD\text{-}EPI} = ACR \times eCER_{CKD\text{-}EPI}$$
$$ePER_{MDRD} = PCR \times eCER_{MDRD}$$
$$ePER_{CKD\text{-}EPI} = PCR \times eCER_{CKD\text{-}EPI}$$
$$eCER_{MDRD}\,(mg/d, male) = 1307.3 + (23.1 \times age) - (0.3 \times age^2)$$
$$eCER_{MDRD}\,(mg/d, female) = 1051.3 + (5.3 \times age) - (0.1 \times age^2).$$
$$eCER_{CKD\text{-}EPI}\,(mg/d, male) = 879.89 + 12.51 \times [weight\,(kg) - 6.19] \times age$$
$$eCER_{CKD\text{-}EPI}\,(mg/d, female) = 879.89 + 12.51 \times [weight\,(kg) - 6.19] \times age - 379.42$$

Urine protein electrophoresis (PEP) was performed with the Minicap Protein 6 kit (Sebia, Lysse, France) according to the manufacturer's instructions [16]. The kit is designed for the separation of six human serum proteins with alkaline buffer (pH 9.9), and the results were reported in percentages of each observed fraction. The albumin fraction was compared with the albumin-to-protein ratio (APR) [11] obtained from the same spot urine specimen.

*Statistical analyses*

Data are expressed as mean ± standard deviation (SD) or frequency (and proportion). Groups were compared using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. The relationship between variables was examined by linear regression. Analyses involving correlations between albuminuria and proteinuria were performed after log transformation of the values due to non-normal distribution. Multiple logistic regression analysis was used to evaluate associations between parameters and diagnosis of glomerular CKD. Two-tailed $P$ <0.05 was considered statistically significant. All statistical analyses were conducted using Statistical Analysis Software (version 9.2; SAS Institute, Cary, NC, USA).

## Results

*General characteristics*

Table 1 shows the general characteristics of our patients. The mean age was 58 years, ranging from 20 to 86 years. Males accounted for 42% of the cohort, and about a half of the patients were diabetic. The mean serum creatinine was 1.7 mg/dL, ranging from 0.6 to 7.4 mg/dL, and the mean estimated glomerular filtra-

**Table 1.** Patient characteristics

| Parameters | Data ($n$=77) |
|---|---|
| Age (years) | 58 ± 18 |
| Sex, male | 32 (42) |
| Diabetes mellitus | 39 (51) |
| Body mass index (kg/m$^2$) | 23.7 ± 3.8 |
| Serum creatinine (mg/dL) | 1.7 ± 1.1 |
| eGFR† (mL/min/1.73 m$^2$) | 50.6 ± 29.8 |
| 24-h urine protein (mg/d) | 1690 ± 3123 |
| 24-h urine albumin (mg/d) | 1099 ± 1910 |
| PCR (g/g) | 2.24 ± 3.68 |
| ACR (mg/g) | 1383 ± 2329 |
| Urine APR (%) | 55 ± 27 |
| Urine PEP-Albumin (%) | 42 ± 28 |
| Biopsy-based diagnosis (%) | 34 (44) |
| ACE inhibitor/ARB use | 44 (57) |

Data are expressed as mean ± standard deviation or as number (percentage). eGFR, estimated glomerular filtration rate; PCR, protein-to-creatinine ratio; ACR, albumin-to-creatinine ratio; APR, albumin-to-protein ratio; PEP, protein electrophoresis; ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; †calculated using the CKD-EPI equation.

tion rate (eGFR) was 50.6 mL/min/1.73m$^2$, ranging from 8 to 125 mL/min/1.73m$^2$. The mean daily proteinuria measured from 24-h urine collection was 1,690 mg/day, ranging from 10 to 15,462 mg/day. The mean daily albuminuria measured from 24-h urine collection was 1,099 mg/day, ranging from 5 to 8,404 mg/day. In 44% of patients, histopathologic diagnosis was based on percutaneous renal biopsy.

**Table 2.** Association between proteinuria and albuminuria from spot urine samples

| | | PCR (mg/g) | | |
|---|---|---|---|---|
| | | < 150 | 150 - 500 | > 500 |
| ACR (mg/g) | < 30 | 13 (16.9) | 1 (1.3) | 0 |
| | 30 - 300 | 6 (7.8) | 13 (16.9) | 2 (2.6) |
| | > 300 | 0 | 2 (2.6) | 40 (52.0) |

$\chi^2$ = 88.59, P < 0.001. Data are expressed as number (percentage). PCR, protein-to-creatinine ratio; ACR, albumin-to-creatinine ratio.

**Table 3.** Association between proteinuria and albuminuria from 24-h urine samples

| | | 24-h urine protein (mg/d) | | |
|---|---|---|---|---|
| | | < 150 | 150 - 500 | > 500 |
| 24-h urine albumin (mg/d) | < 30 | 25 (32.5) | 10 (13.0) | 0 |
| | 30 - 300 | 0 | 3 (3.9) | 1 (1.3) |
| | > 300 | 0 | 2 (2.6) | 36 (46.8) |

$\chi^2$ = 76.25, P < 0.001.

*Correlations between albuminuria and proteinuria*

Fig. 1 shows that ACR significantly correlates with PCR from spot urine samples ($r^2$=0.686, P<0.0001). However, 6 out of 19 patients with PCR < 150 mg/g had microalbuminuria defined as ACR of 30 - 300 mg/g. In contrast, only one out of 14 patients with ACR < 30 mg/g had pathologic proteinuria defined as PCR ≥150 mg/g (Table 2).

The relationship between albuminuria and proteinuria was similar, but varied in 24-h urine samples. Whereas none of 25 patients with proteinuria < 150 mg/d had albuminuria (≥ 30 mg/d), 10 out of 35 patients without albuminuria (< 30 mg/d) had pathologic proteinuria ≥ 150 mg/d (Table 3).

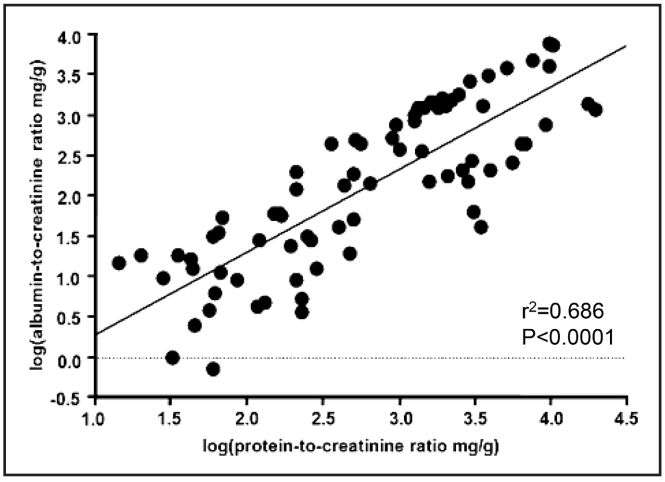


**Fig. 1.** Correlation between protein-to-creatinine ratio (PCR) and album-to-creatinine ration (ACR). Spot urine data show that PCR significantly correlates with ACR.

*Accuracy of ACR and PCR improved by muscle mass adjustment using eCER*

As expected, ACR correlated well with daily albuminuria measured from 24-h urine ($r^2$=0.757, P<0.0001). When ACR was replaced by eAER, the relationship with measured daily albuminuria improved; both $eAER_{MDRD}$ ($r^2$ = 0.951, P<0.0001) and $eAER_{CKD-EPI}$ ($r^2$ = 0.953, P<0.0001) had strong correlations with 24-h urine albuminuria (Fig. 2).

Similarly, PCR correlated with daily proteinuria measured from 24-h urine ($r^2$=0.885, P<0.0001). When PCR was replaced by ePER, the relationship with measured daily proteinuria improved; both $ePER_{MDRD}$ ($r^2$ = 0.893, P<0.0001) and $ePER_{CKD-EPI}$ ($r^2$ = 0.891, P<0.0001) correlated with 24-h urine proteinuria (Fig. 3).

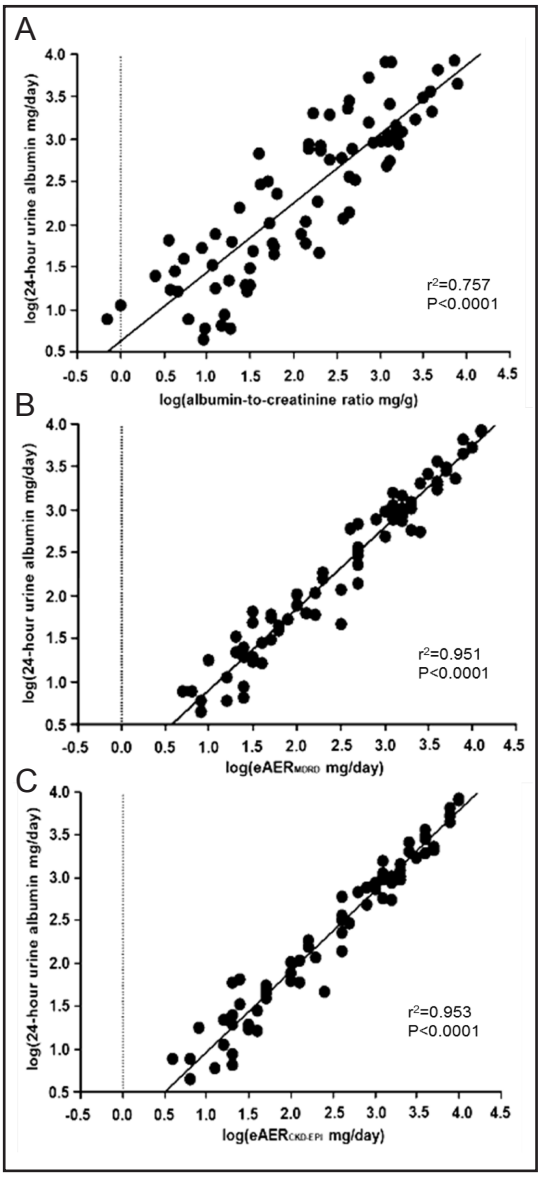


**Fig. 2.** Correlation between 24-h urine albumin and albuminuria estimated from spot urine. As compared with ACR (A), the correlation was improved by estimated albumin excretion rate (eAER) using either the MDRD (B) or CKD-EPI (C) formula.

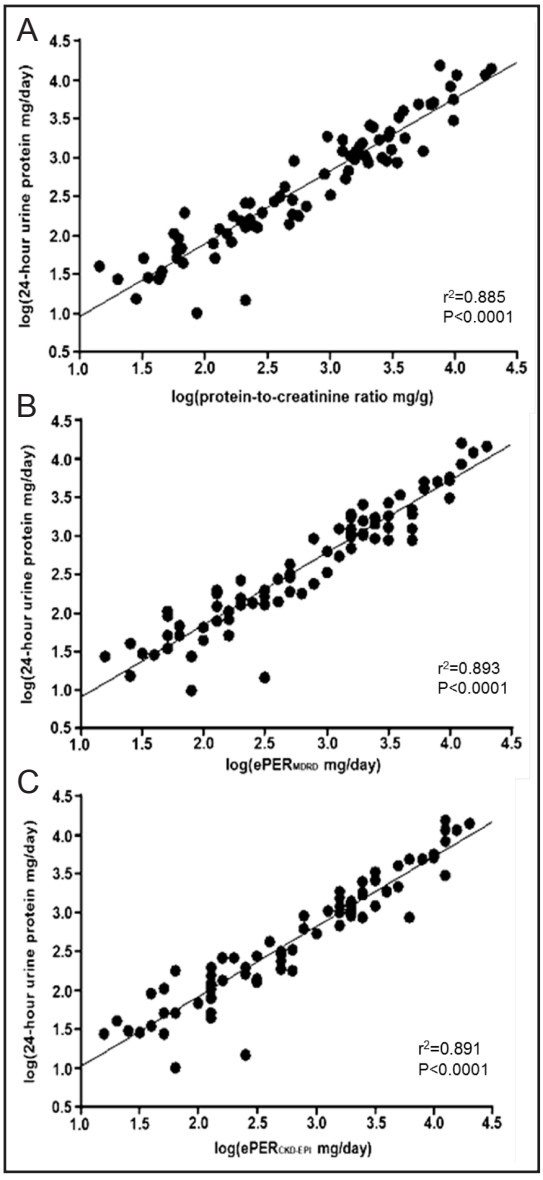


**Fig. 3.** Correlations between 24-h urine protein and proteinuria estimated from spot urine. As compared with PCR (A), the correlation was improved by estimated protein excretion rate (ePER) using either the MDRD (B) or CKD-EPI (C) formula.

*Diagnostic utility of APR in comparison with PEP*

Because urine APR calculated by ACR/PCR represents the percentage of albumin among proteins, it should correlate with the fraction of albumin in urine PEP. As shown in Fig. 4, however, urine APR correlated poorly with the albumin fraction in urine PEP ($r^2$ = 0.33, P<0.0001).

To compare the diagnostic utility of APR and PEP, patients were divided into two groups: glomerulopathy and non-glomerulopathy. Table 4 summarizes the comparison parameters between the groups. Serum creatinine and eGFR were not significantly different. As expected, 24-h urine protein and albumin levels were significantly higher in patients with glomerulopathy (P<0.05). Consistently, PCR and ACR were significantly higher in patients with

glomerulopathy (P<0.05). Whereas APR showed no significant difference between the groups, the albumin fraction obtained from urine PEP was significantly greater in patients with glomerulopathy than in those with non-glomerular CKD (49 ± 24% vs. 11 ± 21%, P<0.05).

Consistent with this, results of multiple logistic regression analysis showed that the albumin fraction in urine PEP was independently associated with glomerulopathy. In contrast, the association between urine APR and PEP was not significant (Fig. 5).

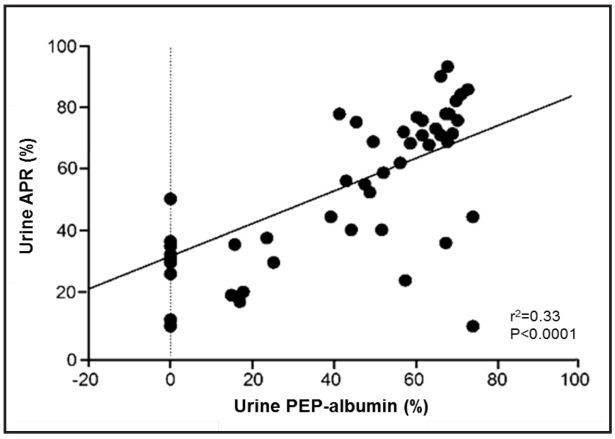


**Fig. 4.** The relationship between spot urine albumin-to-protein ratio (APR) and the percentage of albumin in urine protein electrophoresis (urine PEP-albumin). APR was significantly, but not well correlated with urine PEP-albumin.

## Discussion

In current practices, proteinuria (or albuminuria) is generally quantified from spot urine instead of 24-h urine because many studies, including ours, show high correlations between urine PCR (or ACR) in untimed spot samples and PER (or AER) in 24-h urine specimens [17]. Although 24-h urine proteinuria (or albuminuria) is the gold standard measure for quantitation, accurate urine collection is difficult and inconvenient. Thus, we focused on spot urine markers for quantitative and qualitative analyses of proteinuria.

First, we asked whether measurement of both ACR and PCR is necessary in screening CKD patients. Previously, measuring albuminuria was limited to patients with incipient diabetic nephropathy and hypertension. Also, microalbuminuria is a demonstrated biomarker of endothelial dysfunction. In the Chronic Renal Insufficiency Cohort Study, ACR and PCR were similarly associated with common complications of CKD [18]. According to the recent KDIGO guidelines, however, measurement of albuminuria is preferred to that of total proteinuria in CKD patients [7]. We showed that defining albuminuria by ACR ≥ 30 mg/g was more sensitive than detecting pathologic proteinuria by PCR ≥ 150 mg/g.

**Table 4.** Comparison of parameters between glomerulopathy and non-glomerulopathy

| | Glomerulopathy (n=59) | Non-glomerulopathy (n=18) |
|---|---|---|
| Age (years) | 57 ± 17 | 60 ± 20 |
| Sex, male | 28 (47) | 4 (22) |
| Diabetes mellitus | 33 (56) | 6 (33) |
| Body mass index (kg/m$^2$) | 24.4 ± 3.4* | 21.6 ± 4.5 |
| Serum creatinine (mg/dL) | 1.6 ± 0.9 | 2.1 ± 1.6 |
| eGFR$^\dagger$ (mL/min/1.73m$^2$) | 51.0 ± 27.2 | 38.2 ± 25.1 |
| 24-h urine protein (mg/d) | 2074 ± 3457* | 429 ± 794 |
| 24-h urine albumin (mg/d) | 1352 ± 2096* | 267 ± 610 |
| PCR (g/g) | 2.69 ± 4.06* | 0.73 ± 1.09 |
| ACR (mg/g) | 1682 ± 2564* | 403 ± 699 |
| Urine APR (%) | 58 ± 27 | 46 ± 29 |
| Urine PEP-Albumin (%) | 49 ± 24* | 11 ± 21 |
| Biopsy-based diagnosis (%) | 28 (47) | 6 (38) |
| ACE inhibitor/ARB use | 37 (63) | 7 (44) |

Data are expressed as mean ± standard deviation or as number (percentage). eGFR, estimated glomerular filtration rate; PCR, protein-to-creatinine ratio; ACR, albumin-to-creatinine ratio; APR, albumin-to-protein ratio; PEP, protein electrophoresis; ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; $^\dagger$calculated using the CKD-EPI equation; *P < 0.05 versus non-glomerulopathy.

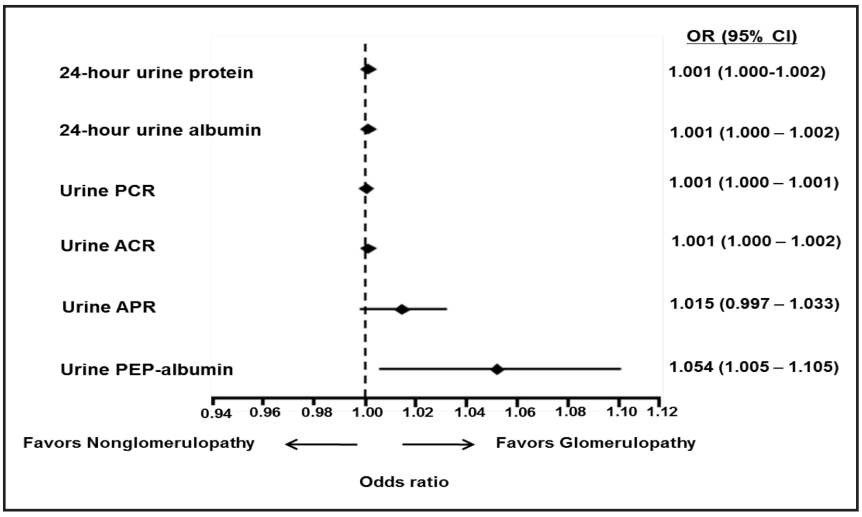


**Fig. 5.** Multiple regression analysis for differentiation between glomerulopathy and non-glomerulopathy. The results show that the albumin fraction in urine protein electrophoresis (urine PEP-albumin) is independently associated with glomerulopathy.

This result may be contradictory to a report by Methven et al. [19], as they concluded that PCR was more sensitive than ACR in predicting clinically relevant proteinuria. They defined 'clinically relevant proteinuria' as ≥ 500 mg/day. On the other hand, we set a PCR threshold of 150 mg/g in this study according to the definition of proteinuria [20]. Thus, we believe that PCR cannot replace ACR for evaluation of proteinuria.

Next, we tested whether the clinical value of ACR and PCR could be increased by modification into eAER and ePER, respectively. Similar to eGFR, ACR and PCR may be adjusted for age and sex because they are actually measures of AER and PER per unit of muscle mass, respectively. In the steady state, urine CER is approximately equal to the creatinine generation rate or muscle mass so that $eCER_{MDRD}$ and $eCER_{CKD\text{-}EPI}$ can be calculated by MDRD and CKD-EPI equation, respectively [12]. Our results showed that compared with ACR and PCR, eAER and ePER were closer to measured 24-h urine albumin and protein, respectively. Thus, the accuracy of ACR and PCR improved after adjusting for muscle mass using eCER. Previous studies have focused on the superiority of eAER over ACR in the accuracy of albuminuria assessment [15, 21]. Automated eAER reporting should be applied to expand the use of eAER in clinical practice [10].

The final question we asked was whether urine PEP could be replaced by APR in the detection of glomerular proteinuria. Urine PEP has been useful in distinguishing between glomerular and tubulointerstitial pathologies [22, 23]. Based on the notion that tubular proteinuria consists of selective low molecular weight proteins, APR was reported to indicate tubulointerstitial disorders such as HIV-associated nephropathy nephritis [11, 24]. On the other hand, the utility of APR was not tested for differentiation of glomerular proteinuria, although glomerular proteinuria mainly consists of albumin. In theory, APR should be in concordance with the percentage of albumin in PEP.

Our results showed that, although significant, APR did not correlate well with the percentage of albumin in PEP (Fig. 4). When we classified our patients into those with and without glomerulopathy, APR was not significant for differentiating glomerular versus non-glomerular CKD. In contrast, the percentage of albumin in PEP was independently associated with glomerular CKD (Fig. 5). In addition to different methodologies between APR and PEP, the following issues may need to be addressed when measuring urine albumin.

An Australasian Expert Group, the Proteinuria Albuminuria Working Group (PAWG), has proposed that ACR be measured in a fresh, first-morning spot sample to screen for proteinuria in CKD [25]. Whereas the method for quantifying total urine protein cannot be standardized because of its variable composition, the international standard reference material for serum albumin measurement was recently adopted for urine albumin measurement, enabling the standardization of urine albumin testing [26]. The cost of immunoassay for albumin measurement should also be considered.

This study was performed at a single center and has limitations due to the small number of enrolled patients. Thus, further studies are required to endorse the use of eAER and ePER instead of ACR, PCR, 24-h urine albuminuria and 24-h urine proteinuria in CKD patients. In addition to urine $\beta_2$-microglubulin, newer tubular markers such as $\alpha_1$-microglobuline, neutrophil gelatinase-associated lipocalin (NGAL), renal liver-type fatty acid binding protein (L-FABP), and kidney injury molecule-1 (KIM-1) will be of help to differentiate tubulointerstitial from glomerular disease [27]. In this study, we have noted the advantages and pitfalls of urinary indices for estimation of albuminuria and proteinuria in patients with CKD, confirming the previous report on diagnostic pathways for the detection and differentiation of renal diseases [28]. About a half of our patients used angiotensin converting enzyme inhibitors or angiotensin receptor blockers to reduce proteinuria and control hypertension. However, we do not believe that our conclusions were affected by these agents because our study was cross-sectional.

## Conclusion

Urine albumin should be quantified because microalbuminuria can be revealed in CKD patients without pathologic proteinuria. In estimating daily proteinuria and albuminuria, ePER and eAER are superior to PCR and ACR, respectively. Although APR may be a simple convenient index, it cannot replace urine PEP for differential diagnosis of glomerular versus tubular proteinuria.

## Disclosure statement

All authors declare that they have no conflict of interest.

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