

Can urinary albumin-creatinine ratio and protein-creatinine ratio be used interchangeably in diagnosis and management of pediatric steroid sensitive nephrotic syndrome?

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Research Article

Keywords: steroid sensitive nephrotic syndrome, protein creatinine ratio (PCR), albumin creatinine ratio (ACR), relapse, remission

Posted Date: January 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8529514/v1>

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Version of Record: A version of this preprint was published at Pediatric Nephrology on September 8th, 2026. See the published version at <https://doi.org/10.1007/s00467-026-07529-7>.

Abstract

Background:

In pediatric nephrotic syndrome (NS), conventionally, spot urinary protein-creatinine ratio (PCR) is used for diagnosis, and to define relapse and remission. This study evaluates whether urine albumin-creatinine ratio (ACR) can reliably predict proteinuria status to manage NS according to existing PCR guidelines

Methods:

Children between 1 to 18 years of age with steroid sensitive NS were included. Blood samples for albumin, creatinine and morning urine samples for albumin, total protein and creatinine were taken, PCR and ACR were calculated in mg/mg. Data obtained was randomly split into training (70%) and test (30%) cohorts. Data was bootstrapped 100,000 times, a linear regression model predicting ACR from PCR was fit to the training cohort, and the ACR cut-offs for NS relapse and remission were derived from conventional PCR thresholds. Finally, the model's accuracy was validated using the test cohort.

Results:

In 202 patients (median age 7.4 years, 63% male, normal creatinine for age), ACR and PCR were highly correlated with $r_s=0.97$. In the training cohort, the final regression equation was estimated as $ACR = 0.76(PCR) - 0.06$. Using this, PCR values of 2 mg/mg and 0.2 mg/mg yielded ACR cut-offs of 1.46 mg/mg (relapse) and 0.09 mg/mg (remission) respectively. In the test cohort, these cut-offs showed high diagnostic accuracy, with sensitivities of 97–100% and specificity of 96%

Conclusion:

Our data shows very strong correlation between spot urinary ACR and PCR in children with steroid sensitive NS. The ACR cut-offs obtained can be useful in diagnosis and follow-up of SSNS, or in evaluating retrospective study data, when ACR is available rather than PCR.

Introduction

Nephrotic Syndrome is the most common chronic / recurring kidney disease in childhood [1]. More than 85% of affected patients respond to steroids but may have repeated relapses. The confirmation of diagnosis includes demonstration of nephrotic range proteinuria. While 24 hour urine protein excretion is considered the gold standard for estimating degree of proteinuria, there are often errors in completeness of collection and the limitations of collecting 24 hour urine samples in children are well recognized. Current international guidelines accept protein : creatinine ratios (PCR) from an early morning spot urinary sample to be representative [2, 3], and studies have shown good correlations between 24 hour urinary protein excretion and PCR [4, 5]. By convention, urinary PCR has become an important criteria to

diagnose pediatric nephrotic syndrome (NS), and is also used to define relapse and remission in NS [2, 3, 6].

While PCR estimation is frequently used in the management of glomerular diseases in children, it is not such a common test in adult medicine. Overall, in the general population, albumin : creatinine ratios (ACR) are more widely used, particularly for the detection of subtle kidney injury or disease, and for categorization into chronic kidney disease (CKD) stages [7, 8]. Technically ACR is a more precise, and reproducible test than PCR [8]. In many regions, especially in extra-institutional and peripheral laboratories, ACR techniques are better known, and patients in our national practice, will often return with an ACR report when they have been prescribed a PCR test. Since proteinuria categorization criteria in NS warrants PCR estimation, this technically requires re-testing, requiring added time and expense.

Our current study thus aims to investigate if there are direct strong correlations between spot urinary PCR and ACR in children with steroid sensitive NS, and whether the two parameters can be used interchangeably for the diagnosis and management of pediatric NS.

Methods

A cross sectional study was performed in children aged 1 to 18 years with previously diagnosed steroid sensitive NS. Patients attending kidney clinics and admitted to inpatient wards in a single tertiary level hospital, were invited to participate after due informed consent and assent (where applicable) process.

Patients with acute complications like UTI, AKI, thrombosis, other glomerulopathies like IgAN, SLE, vasculitis, Alports syndrome, CKD Grades 3 to 5 or on dialysis / transplanted, steroid resistant NS, congenital anomalies of kidney and urinary tract (CAKUT), known tubular diseases, other acute or chronic non-renal systemic diseases were excluded.

Demographic and clinical details were noted for all patients. Blood samples were taken for serum creatinine and albumin. Early morning spot urine samples (from the first or second urine passed) were collected and tested for proteinuria by dipsticks, PCR and ACR tests.

As per current international guidelines, PCR cut-off levels of ≤ 0.2 mg/mg to diagnose NS Remission and ≥ 2 mg/mg to diagnose NS Relapse were considered as standard.

Biochemical Analysis:

All samples were tested in the biochemical lab of the institute.

The dipstick used was the commercially available URiSCAN Sysmex,(Model:UC3500), utilizing colorimetric reaction with stated semiquantitative urine albumin assessment of:

Negative -no albumin

Trace – between 15 and 30 mg/dL

1+ – between 30 and 100 mg/dL

2+ – between 100 and 300 mg/dL

3+ – between 300 and 1000 mg/dL

4+ – >1000 mg/dL

The serum and urine creatinine levels were quantified by IDMS traceable compensated Jaffe's method (COBA 6000), with COV < 5%.

Serum albumin levels were quantitatively assessed by bromocresol green method on the Roche/Hitachi Cobas 6000 which has COV of < 5%,

Urine albumin and urine total protein levels were quantitatively assessed by Immunoturbidimetric assay on the Roche/Hitachi Cobas 6000 which has COV of < 5%.

Where urine albumin value was > 40 mg/dL and urine protein > 200 mg/dL, the urine sample was diluted with normal saline solution in 1:30 ratio.

The urinary PCR and ACR ratios were calculated in mg/mg.

Sample size estimation : Prior studies have estimated ACR from PCR values, compared calculated ACR with measured ACR and examined ACR and PCR correlations with ability to predict CKD progression, in general populations and in patients with CKD [9–15]. However such associations have not been examined in a restricted patient cohort of steroid sensitive NS. Since this group is expected to have highly selective but high grade albuminuria in relapse, their results are likely to be different from the previous cohorts studied. We have therefore treated this as a pilot study including practically feasible numbers and aimed to include approximately 200 patients in the study.

Statistical Analysis:

Categorical variables are expressed as numbers and percentages. Continuous variables were checked for normal distribution with the Shapiro-Wilk and Kolmogorov-Smirnov tests. Since the majority showed non-normal distributions the data is summarized with median and inter-quartile range. Association between continuous variables is captured by Spearman's rank correlation coefficient.

For the main analysis focusing on finding the ACR cut-off that would define remission and relapse, we opted to split the data into training and test samples. Seventy percent of the observations were randomly selected to be included in the training set whereas the remaining thirty percent comprised the test set. To reduce estimation error, the training data set was bootstrapped 100000 times nonparametrically. For each bootstrapped sample, three things were created:

- A simple linear regression equation with ACR as the dependent and PCR as the independent variable.
- Predicted value of ACR with a plug-in PCR value of 2 mg/mg. This would be the estimated relapse cut-off based on ACR.
- Predicted value of ACR with a plug-in PCR value of 0.2 mg/mg. This would be the estimated remission cut-off based on ACR.

These results are further analyzed using diagnostic test accuracy evaluation parameters in the test data set.

The programming and analyses were carried out in R version 4.2.2 [16].

Ethics Approval

was obtained from the CMRI Institutional Ethics committee. The study was funded by CMRI internal research funds.

Results

A total of 202 patients were included in the study. Their median age was 7.42 (IQR 4.92, 10.58) years and 128 (63.4%) were male. The median serum albumin was 3.23 (2.29, 3.99) g/dl and serum creatinine 0.36 (0.3, 0.46) mg/dl, with all patients having normal serum creatinine for age. The median spot urine PCR was 2.79 (0.31, 8.37) mg/mg while the median spot urine ACR was 2.064 (0.064, 5.3) mg/mg. The distribution of dipstick proteinuria, ACR and PCR data is shown in Table 1.

The spot urine ACR and PCR values showed highly significant correlations with $r_s = 0.966$ (Fig. 1).

In the random 141 patients (70%) taken as the training cohort, the regression equation of ACR vs PCR based on 100000 bootstrapped samples was $ACR = 0.76(PCR) - 0.06$, where we used as the intercept and slope estimates, the median of the 100000 bootstrapped values.

The plug-in PCR values of 2 mg/mg and 0.2 mg/mg yielded the histograms of the bootstrapped ACR cut-offs for relapse and remission as shown in Fig. 2, with median ACR cut-offs of 1.46 mg/mg for relapse and 0.09 mg/mg for remission. These histograms estimate the empirical distributions of the respective cut-offs and provide an assessment of the error in generating these estimates.

Using these cut-offs, the diagnostic test evaluation findings on the remaining test set of 61 patients are given in Table 2.

Discussion

Steroid sensitive NS is commonly due to underlying minimal change disease, and characterized by selective proteinuria : mainly consisting of the relatively smaller molecular weight protein -albumin [17].

In keeping with this pathophysiology, our study shows a very strong correlation between spot urinary ACR and PCR in children with SSNS, with a correlation coefficient = 0.97. The linear regression equation predicting ACR from PCR values yields ACR cut-offs of 0.09 and 1.46 mg/mg to correspond to PCRs of 0.2 and 2 mg/mg (accepted criteria for defining NS remission and relapse) respectively in our training cohort. The diagnostic accuracy estimation for these cut-off values in our testing cohort, reveals high degrees of specificity and sensitivity.

While urinary dipsticks are easily available and useful for home proteinuria screening, they are imprecise, being only semiquantitative in nature, and results vary depending on urinary concentration. Assays of urine albumin or urine protein are also subject to variations due to the concentration of urine; however, such errors can be diminished by using ratios with creatinine as the denominator. In paediatric practice, PCR is usually used as the screening tool for quantitative evaluation of proteinuria for diagnosis, planning management, and assessing response in glomerular diseases. Generally, PCR is preferred over ACR in glomerular pathologies causing non-selective proteinuria when there is excretion of both small and large molecular weight proteins. In tubular proteinuria also, PCR is preferred over ACR as a screening test, although estimation of tubular proteins is more specific. [8, 18, 19, 20]

In contrast, ACR is the preferred reference value used for assessment of subtle renal pathology, particularly in diabetic adults, and at all ages, for categorisation of CKD [7, 8]. Assaying urinary albumin provides more sensitive and specific measures of glomerular permeability than urinary total protein [8, 21]. Therefore, technically ACR is deemed to be the superior test with more precise and reproducible results from different laboratories. It is particularly more sensitive for lower degrees of proteinuria and the detection of persistent microalbuminuria (30 to 300mg/g), which is deemed an important risk for CKD. However, costs of measuring urinary total protein may be lower than those for measuring albumin, making ACR the more expensive measure [8, 13, 21].

In practice, there is often a great deal of confusion between these two parameters. Many labs in India and other under – resourced regions are un-accustomed to PCR tests even when it is specifically asked for and will provide an ACR report instead. Although currently ACR cannot replace PCR estimation in children with NS, in such cases, rather than repeat testing, we suggest that the ACR cutoff values obtained in the current study can be used to indicate status in steroid sensitive NS. Likewise, these cut-offs obtained may be used for interpretation in retrospective studies when only ACR values may be available.

Previous studies estimating ACR from PCR values with the use of conversion equations, have been performed in large populations as well as in patients with CKD [9, 10, 11]. They found that estimated ACR and measured ACR differed more at lower values. Similarly, the association between PCR and ACR was in-consistent for PCR values less than 50 mg/g, while for higher PCR values, the equations demonstrated moderate sensitivity and specificity for screening and classification into CKD stages [10]. In children [12] and adults [13, 14, 15] with CKD, the utility of ACR and PCR were similar in predicting CKD outcomes.

Our study differs from the above studies in including only confirmed steroid sensitive NS patients, expected to have high grades of selective albuminuria during relapse. Thus the potential concern of missing non-albumin proteins is minimal in this cohort. In our study, rather than precise conversion of urinary ACR to PCR, we opted to detect ACR cut-off values to define NS relapse and remission, as this is the clinically relevant issue. However, we too found higher concordance of ACR and PCR at greater values of proteinuria (i.e. with relapse cut-off) than at lower values (Table 1).

Limitations and Strengths:

1. As a pilot study, our included numbers are low compared to prior population based studies. It is likely that if numbers are significantly increased, the regression equation as well as the cut-off values will be slightly different. We have addressed this issue by using statistical methods that will minimize variability between samples.
2. Biochemical tests in different labs can give variable results depending on technique and reagents used [21]. Our study utilizing a quantitative immuno-turbidimetric method, based on specific antigen-antibody binding, for both ACR & PCR ensures that positive interferences are practically nullified and accurate values for both parameters obtained. However, larger studies performed in different centers are required to confirm our results.
3. Our results are acknowledged to be more in concordance at higher levels of proteinuria (thus more accurate in prediction of relapse).
4. Our results only pertain to patients with steroid sensitive NS and may be different in conditions where non-selective or tubular proteinuria occurs

Conclusions

our study yields ACR cut-off values of 0.09 mg/mg (90 mg/g) and 1.46 mg/mg (1460 mg/g) for detecting NS remission and relapse that correspond to PCR values of 0.2 and 2 mg/mg respectively. These results will be useful in clinical diagnosis and follow-up of SSNS, or in evaluating retrospective study data, when ACR levels are available rather than PCR levels. Our results need confirmation from larger multicenter studies.

Declarations

Contributions:

SB conceptualized the study, AS directed study design and statistical analysis, SS supervised biochemical analyses, IP and AG collected clinical and biochemical data. SB, AS and SS wrote the initial draft while all authors edited and reviewed the manuscript.

Data availability:

All data is available with the authors on reasonable request.

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Tables

Table 1
Spot Urine data (n = 202)

Dipstick	Negative or Trace	1 + or 2+	3 + or 4+
No of patients	51 (25%)	74 (37%)	77 (38%)
Spot Urine PCR (mg/mg)	≤ 0.2	> 0.2 < 2.0	≥ 2.0
No of patients	39 (19%)	50 (25%)	113 (56%)
Spot Urine ACR	≤ 0.09	> 0.09 < 1.46	≥ 1.46
No of patients	52 (26%)	37 (18%)	113 (56%)

Table 2
Diagnostic Test evaluation in Test Cohort (n = 61)

Performance Metric	Relapse	Remission
Sensitivity	35/36 = 97.2%	10/10 = 100%
Specificity	24/25 = 96%	49/51 = 96.1%
Positive Likelihood Ratio	24.3	25.6
Negative Likelihood Ratio	0.03	0

Figures

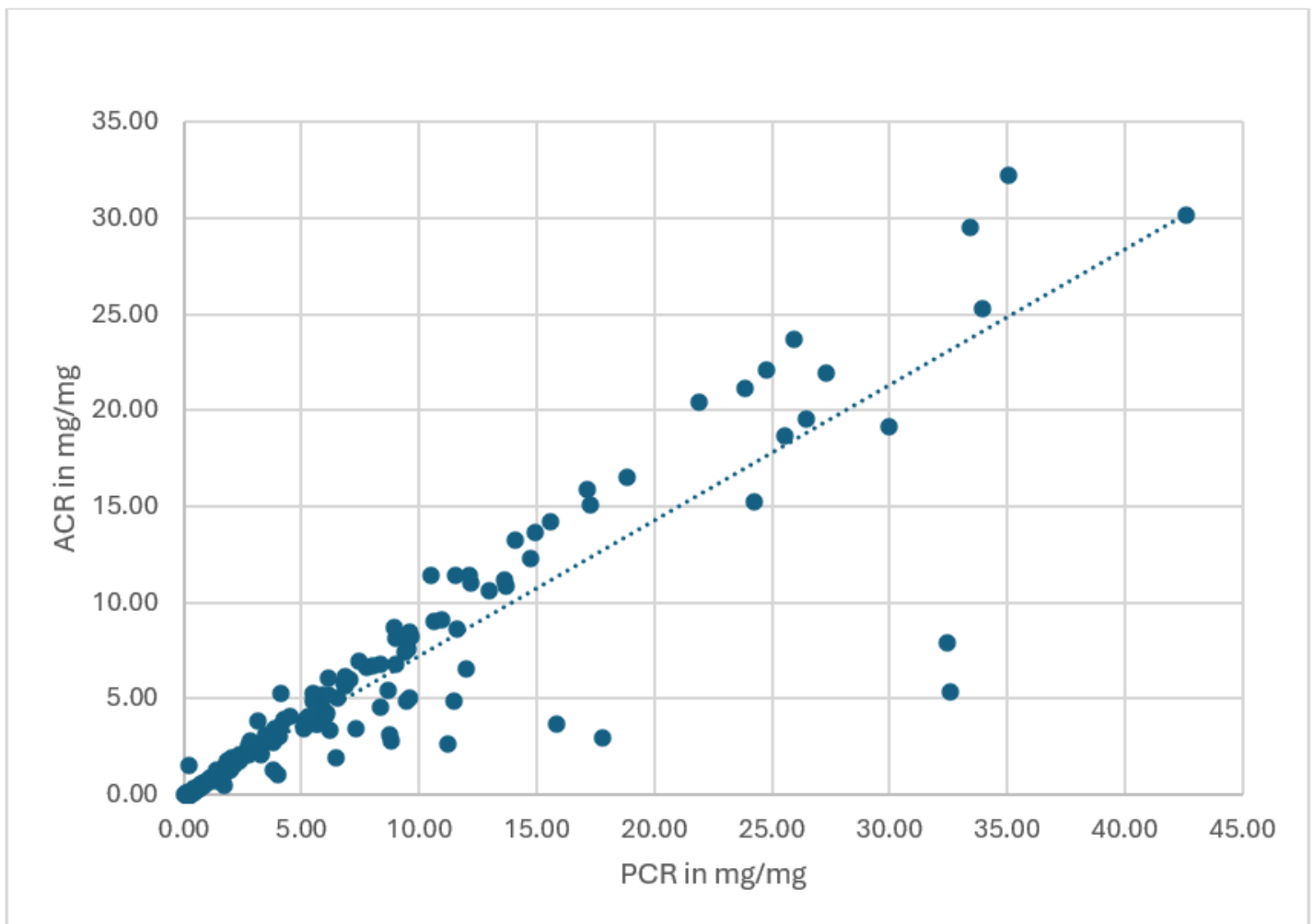


Figure 1

Correlation of spot urinary ACR to PCR

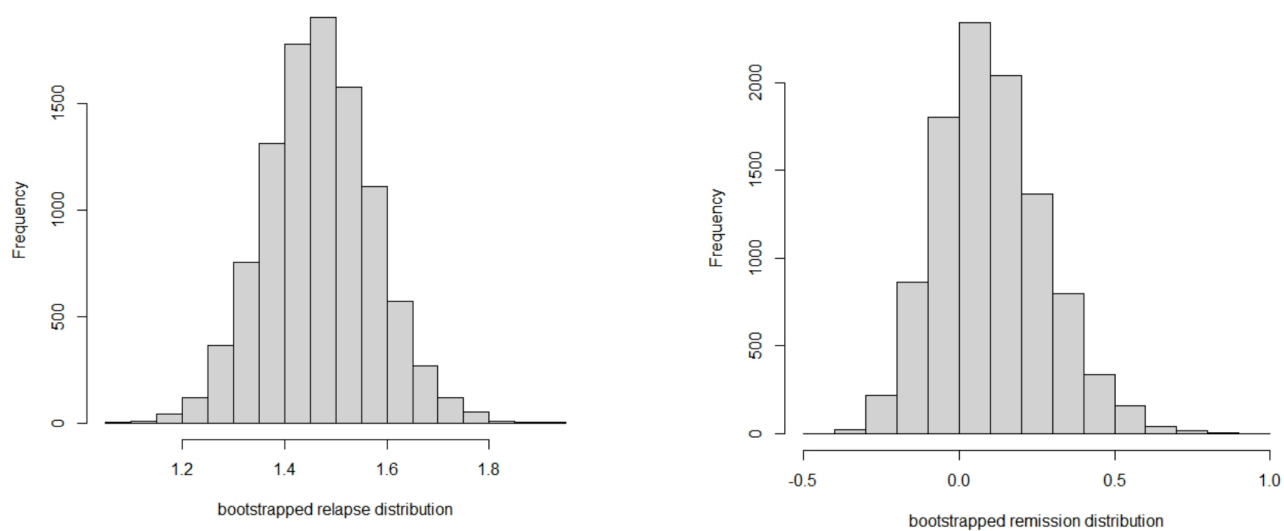


Figure 2

Histograms of the bootstrapped ACR cut-offs for relapse and remission in the Training Cohort