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Correlation between spot urine protein creatinine ratio and 24-hour urinary protein in systemic lupus erythematosus patients with proteinuria

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Abstract

Introduction: All patients with Systemic Lupus Erythematosus(SLE) should be evaluated for proteinuria. Twenty-four hour urinary protein (24hUP) is the gold standard to quantify proteinuria but is cumbersome and is sometimes inaccurate. Spot urine protein creatinine ratio (UPCR) is a simple, convenient method to quantify proteinuria. This study aims to analyse its utility as a screening tool and ability to accurately measure proteinuria against 24 hUP was determined.

Method: This was a cross sectional study. Eighty-seven patients with lupus with proteinuria on urinalysis were enrolled. Proteinuria was quantified using UPCR and 24 hUP. A prospective, analytical and observational study was done for a year. Sensitivity, specificity, correlation and agreement analysis between UPCR and 24 hUP was done. The best cutoff points for UPCR predicting a 24 hUP of 0.5, 1.0 and 3.0 g/day were determined using receiver operating characteristic curve.

Result: The Sensitivity and specificity of UPCR were 97% and 29.1%, respectively. All samples' correlation was high but negligible to low at lower range proteinuria, i.e.≤ 3gram/day and high at >3 g/day. Agreement for all samples, as well as for different levels of proteinuria, was poor. Cutoff points for optimal sensitivity and specificity of UPCR predicting 24hUP of 0.5, 1.0, and 3 g/day was 0.8, 1.55, and 4.5 g/g, respectively.

Conclusion: With sensitivity of 97%, UPCR can be used as a screening test for proteinuria. However, due to poor specificity of UPCR and poor agreement, the accurate level of proteinuria should be measured by 24hUP.

Keywords: Spot Urine Protein Creatinine Ratio, Systemic Lupus Erythematosus, Twenty-Four-Hour Urinary Protein

INTRODUCTION

Systemic Lupus Erythematosus (SLE) affects the kidneys in about 50% of patients. Its prevalence varies considerably between different regions, ranging from 4.8-78.5 in the USA and Canada, 25-91 in Europe, 30-50 in China and 9-18 in Japan per 100000 population.[1] Well conducted, high-quality clinical and epidemiological studies to describe the distribution of disease and the outcomes of treatment within the ethnic and geographic diversity of Nepal are lacking.[2] Sitaula et al. report that the kidney is the most commonly affected system, involving 60.6% of the patient population in a tertiary hospital in central Nepal.[3]

Lupus nephritis (LN) is a significant cause of morbidity and mortality in SLE.[4] The most affected are females younger than 50 years.[5] Diagnosis of LN can be challenging, being clinically subtle, and is discovered mainly by urinalysis. Therefore, Proteinuria, which manifests in almost all Lupus Nephritis patients, should be evaluated in all SLE patients even if asymptomatic at diagnosis and then yearly or in proteinuric flares by urinalysis as it correlates with glomerulonephritis and guides diagnostic as well as therapeutic decisions.[1,6] Among the quantification methods, the gold standard is 24-hour urinary protein, which is cumbersome and sometimes inaccurate.[7] However, the accuracy of the more convenient spot urine protein creatinine ratio in SLE remains unclear.[8,9] This study determined the accuracy of routinely used simpler and convenient UPCR in relation to 24 hUP so that further along, it can reliably guide diagnostic and therapeutic decision in SLE patients with proteinuria.

METHOD

This was a prospective, analytical and observational study. The objectives were to find out the utility of spot Urine Protein creatinine ratio as a screening tool by determining its sensitivity against 24-hour urinary protein and also to find out the accuracy by conducting correlation and agreement analysis between them. The study was done in Patan Hospital from March 2021 to February 2022. Ethical approval was obtained from the institutional review committee of the Patan Academy of Health Sciences (IRC-PAHS). Written consent was obtained from the patient/legal guardian.The confidentiality of the patient was maintained throughout the study and analysis. Data was collected in Proforma and entered in a form created in Microsoft Excel ona password-protected computer. Since the relevant investigations are all part of the workup for patients with SLE, no additional costs were borne by patients due to this study.

All patients more than or equal to 14 years old who fulfilled 1997 American College of Rheumatology criteria for SLE and with evidence of Proteinuria either new or while on treatment on urine routine analysis, i.e., Urine Albumin: Trace or more or those undergoing treatment for SLE and being followed up at Patan Hospital were included.[10] Pregnant females, patients on dialysis or with Stage 5 kidney disease and those who have undergone a kidney transplant were excluded from the study.

Patients were instructed to provide urine samples at their convenience for protein creatinine ratio but were instructed to collect the 24-hour urinary protein starting the same day or the very next day. Patients were instructed to empty the bladder and discard the urine, and from that point onward for 24 hours, all urine was to be saved in the container. At the end of that 24-hour period, the bladder was emptied, and that urine was saved. Convenience sampling was done.

The sample size was calculated using the following formula:
$(Z^2_{1-\alpha/2} \times S_N \times (1- S_N))/(L^2 \times P)=(1.96)^2 \times 0.85(1-0.85)/(0.1^2 \times .606)=81$

Where,
Z= standard normal deviate corresponding to the specified size of critical region(α)=1.96
α= size of critical region (1- α is confidence level)=0.05
Sensitivity and prevalence were determined from other studies.[3,8]

Data was collected per proforma and entered into a spreadsheet using Microsoft Excel. Age, sex, serum creatinine, total duration of illness, urine albumin, urine for spot protein creatinine ratio and 24-hour urinary protein were recorded. Microsoft Excel and EZR software (R-based programming software, version 1.50) were used for data analysis. The Kolmogorov-Smirnov (KS) test tested all input variables for normal distribution. Mean with standard deviation was used for normal distribution and median with range for skewed distribution. Other analyses were done based on specific objectives and pre-specified dummy tables. Delong statistics were used for ROC analysis, and the sum of sensitivity and specificity was used to determine the optimal cutoff. Some of the ROC analyses were done with the help of EasyROC, a web-based software. Additional and sub-group analyses were done based on the data. The sensitivity (Sn) and specificity (Sp) of urine protein creatinine ratio against 24 hr urinary protein was analysed using a 2×2 contingency table. The Correlation Coefficient between them was determined and interpreted as follows: 0.00–0.29 = negligible, 0.3–0.49 = low, 0.5–0.7 =moderate, 0.7–0.9 = high, and 0.9–0.99 = very high.

Agreement between them was determined by Lin's Concordance correlation coefficient and interpreted as: <0.9=Poor, 0.9-0.95=moderate, 0.95-0.99=substantial and > 0.99=Almost perfect.

RESULT

The study contained total of 87 participants. Among the total participants 84(96.5%) were female. The demographic of patient is shown in the Table 1.

Table 1. Baseline Characteristics of patients involved in the study

Characteristics	Values
Age Distribution	
Mean Age (SD)	30.55 yrs (10.99)
Sex	
Female (%)	84(96.5%)
Male (%)	3(3.5%)
Labaratory characteristics	
Creatinine (Quartiles)	0.7(0.6-0.9) mg%
Disease duration (quartiles)	2.00(1-3.75) years
Urine protein creatinine ratio(quartiles)	1.65(0.9-4.645) g/g
24-hour urinary protein(quartiles)	1.012(.435-3.23) g/day

To determine sensitivity and sensitivity of UPCR against 24hUP, a 2×2 contingency table is constructed and depicted in Table 2. As 24-hour urinary protein of 0.5 g/day proteinuria is considered significant, it is plotted against its equivalent spot urine protein creatinine ratio of 0.5 g/g.[6, 17]

Sensitivity of UPCR= 61/ (61+2) × 100= 97%
Specificity of UPCR= 7(7+17) × 100= 29.1%

Table 2. Two-by-two Contingency table between UPCR & 24 hUP

	24 hUP + *	24 hUP - **
UPCR + #	61	17
UPCR - ##	2	7

#Presence of significant proteinuria in spot urine protein creatinine ratio i.e.>=0.5 g/g; ##Absence of significant proteinuria in spot urine protein creatinine ratio i.e.<0.5g/g; *Presence of significant proteinuria in 24-hour urinary protein i.e.>=0.5 g/day; **Absence of significant proteinuria in 24-hour urinary protein i.e.<0.5 g/day

Correlation between UPCR and 24hUP was 0.86 which was interpreted as high. Agreement analysis between UPCR and 24hUP was done using Lin's concordance correlation coefficient. It was 0.78 which was interpreted as poor (Table 3).

Table 3. Correlation and agreement between UPCR and 24 hUP

Correlation Coefficient	Values
Spearman correlation coefficient	0.86
Lin's concordance correlation coefficient	0.78

Correlation was poor at lower level of proteinuria(≤3g/day) and high at higher level of proteinuria(>3g/day) as determined using Spearman correlation coefficient. Agreement was poor at all levels of proteinuria as determined using Lin's concordance correlation coefficient (Table 4).

Table 4. Correlation and agreement between UPCR and 24 hUP at varying Levels of proteinuria

24 hUP (number of samples)	Spearman correlation coefficient (p value)	Lin's concordance correlation coefficient
<0.5g/day(24)	0.09(0.67)	0
0.5-1g/day (19)	0.251(0.2995)	0.022
≥1-3g/day(21)	0.47(0.0016)	0.22
>3g/day(23)	0.8(<0.0001)	0.69

Optimal cutoff point of UPCR for 24 hUP of 0.5g/ day was determined which was 1.42g/g with Sensitivity of 95.8% and specificity of 71.4% (Fig 1).

Optimal cutoff point of UPCR for 24 hUP of 1g/day was determined which was 1.55g/g with sensitivity of 85.7% and specificity of 86.7% (Fig 2).

Optimal cutoff point of UPCR for 24 hUP of 3g/day was determined which was 4.5g/g with sensitivity of 96.9% and specificity of 91.3% (Fig 3).

DISCUSSION

Proteinuria is one of the most critical manifestations of SLE for diagnosing LN, monitoring disease activity, and prognosis.[11,12] Therefore, quantifying proteinuria in the most accurate way is of utmost importance. Among various proteinuria quantification methods, 24hUP is considered the gold standard in Lupus nephritis. However, there are major limitations to 24hUP. First of all, it is time-consuming and cumbersome. Also, there is a chance of under-collection or over-collection of samples. Therefore, nowadays, UPCR has become a widely accepted method of quantification of proteinuria as it is simple, more convenient, and widely available. It is routinely used in clinical practice, research settings, and clinical trials.[13,14] Therefore, this study was conducted to determine the utility of a simple,

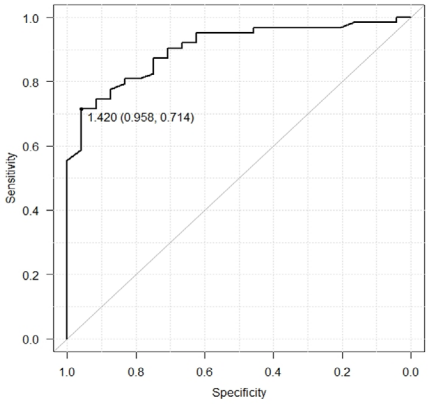

Figure 1. ROC curve to determine UPCR for UPCR for 24hUP of 0.5g/day

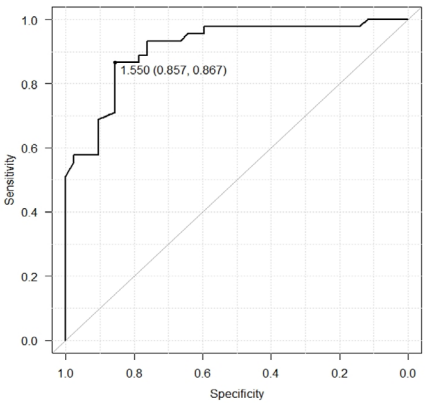

Figure 2. ROC curve to determine UPCR for 24hUP of 1g/day

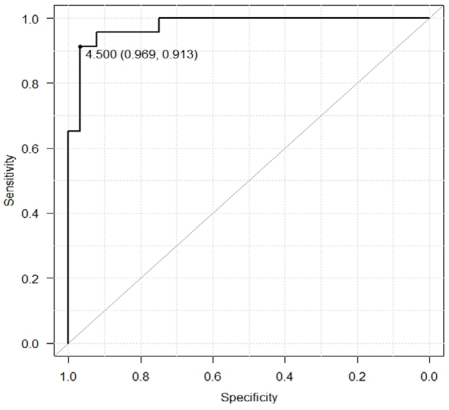

Figure 3. ROC curve to determine 24hUP of 3g/day

widely available, inexpensive test in the quantification of proteinuria so that, further along, it will be helpful for the physicians to make diagnostic as well as therapeutic decisions.

SLE is an autoimmune disease which is much more common in females, especially those of reproductive age, which include more than 90% of the total patients.[1] The demographic profile of patients in the study was also similar, with almost 97% of the patients being female and of the reproductive age group (30 years). As the prepubertal age group population where the ratio of male and female lupus patients is almost similar was excluded from the study, the ratio of female and male population even got higher.[15] It is also likely that most patients with SLE will have kidney involvement within 5 years of diagnosis, or LN may be the first presentation of SLE. Likewise, the study population had evidence of proteinuria within a median of 2 years of diagnosis, which is within the time frame of developing LN.[16]

Most of the patients had creatinine within the normal range, suggesting the kidney may not be involved in some cases, or if involved, it was in an early stage or there was a good response to treatment. The median UPCR was higher than the median 24hUP, suggesting overestimations of proteinuria with this test in this study, which was analyzed further. It was evaluated by constructing a 2×2 contingency table. It calculated the sensitivity and specificity of UPCR against 24 hUP of 0.5 g/day, which is considered significant proteinuria, and a diagnostic and therapeutic decision has to be made. Some even consider a kidney biopsy at this level of proteinuria.[6,17] Sensitivity and Specificity thus calculated were 97% and 29.1% respectively, which clearly shows that UPCR overestimated proteinuria in this study. A similar study done by Medina Rosas et al. found sensitivity to be 91% and Specificity to be 83% of UPCR of 0.5g/g vs 24 hUP of 0.5 g/day.[9] Similarly, Choi et al determined sensitivity to be 91.2 % and specificity to be 70%.[8] Therefore, both study showed comparable sensitivity with contrast in specificity.

Since it was demonstrated that UPCR overestimated proteinuria with an unacceptable level of specificity, optimal cutoff points of UPCR corresponding to 24 hUP of 0.5 gm/day proteinuria were determined. Also, optimal cutoff points of higher levels of proteinuria, i.e 1g/day and 3 g/day, were defined as a higher degree of proteinuria correlates with more severe disease activity. This was determined using the ROC curve. UPCR of 1.42 g/g determined 0.5g/day proteinuria with Sn 71.4% and specificity of 95.8%. However, higher sensitivity compromising specificity is more desirable as it is of utmost importance that patients with significant proteinuria are not missed. It was found that a UPCR of 0.8g/g would reflect 0.5 g/day proteinuria with 95.23% Sn and 62.5% Sp. UPCR of 1.55 g/g and 4.5 g/g was the optimal cutoff point for 1g/day and 3g/day proteinuria, respectively. Leung et al.. determined cut-off points for 0.5, 1 and 3.5 g/day to be 0.45, 0.7 and 1.85 g/g, respectively.[18]

Correlation and agreement are two different concepts for a new test. The concerned test has to demonstrate agreement with the gold standard to replace the test.[19] Although the correlation between UPCR and 24hUP for all samples was high (0.86), agreement between the samples was poor (0.78), indicating its limitation of use as a substitute test of 24hUP. Medina Rosas et al. similarly found the correlation high but agreed that the agreement between the two tests was poor.[9] Zheng et al. found the correlation high and the agreement reasonably good between the two tests.[20] Choi et al. found the correlation to be high and the agreement to be good.[8] Birmingham et al. studied 64 patients with SLE and showed a moderate correlation and weak agreement for samples between 0.5 and 3.0 g/day.[21]

While correlation was high while taking all samples, it became negligible with lower range of proteinuria i.e.≤1g/day proteinuria where clinicians need to be alert about kidney involvement. It was 0.09 for <0.5g/day and 0.251 for 0.5-1g/day proteinuria. However, the results weren't statistically significant. It improved but was still poor for 1-3 g/day proteinuria while it was high for >3g/day proteinuria. Agreement analysis done at all range of proteinuria was poor. Medina Rosas et al similarly found low- negligible correlation at proteinuria <2 g/day while moderate correlation at proteinuria >2g/day. Agreement was also poor at all levels of proteinuria using Lin's concordance coefficient.[9]

Although the UPCR correlates well with 24-hour urine protein excretion on the population level, its usefulness in predicting the true 24-hour protein excretion in any given individual is debatable. The major limitation of UPCR is that it is heavily influenced by urine creatinine concentration, and variation of protein excretion can occur throughout the day, mainly resulting from exercise and posture.[22] UPCR is an accurate estimate of 24-hour proteinuria in someone who excretes 1000 mg/day creatinine or in the mean population who excretes 1g/day creatinine. However, creatinine excretion in a population can vary substantially.[23,24] In individuals with large muscle mass, creatinine excretion may be much higher than 1g/day, and UPCR will underestimate proteinuria. However, in a cachectic patient with small muscle mass, creatinine excretion may be much lower than 1g/day, and UPCR will overestimate proteinuria. In our study, UPCR has overestimated proteinuria, which could be due to lower daily urine creatinine excretion, which was not evaluated. Similarly, patients could be on medications like cotrimoxazole, which could influence urine creatinine excretion.[25]

CONCLUSION

Lupus Nephritis is subclinical in most cases manifesting only as proteinuria. Proteinuria is evaluated using tools like urinalysis, UPCR and 24hUP. Therefore, clinicians should rely heavily on the validity and reliability of these tools to make diagnostic decisions, like performing kidney biopsies

or initiating and modifying treatment based on the result. This study tried to compare the accuracy of simpler method like UPCR against cumbersome but gold standard method 24hUP. On the basis of our results, it can be concluded that UPCR can be used as a practical screening test to rule out significant proteinuria without doing cumbersome 24 hUP. However due to low specificity as well as negligible agreement, it doesn't precisely reflect 24-hour urinary protein, abnormal values especially indicating the lower range of proteinuria require confirmation.

DECLARATIONS

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Conflict of Interest
I don't have any conflicts of interest.

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Ethical Clearance
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Consent for Study
Written informed consent was taken from the patient or, if the patient was a minor, from the parents.

Consent of Publication from Authors
All the author/s and participants are consented for publication of the findings.

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