



Original Research Article

Evaluation of spot urinary protein creatinine ratio for quantification of proteinuria in women with hypertension in pregnancy: A prospective observational study

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ABSTRACT

Objective: To calculate the cut off value of the spot urine protein/creatinine ratio (PCR) for predicting significant proteinuria in our population of patients with HTN (hypertension) in pregnancy, and study its correlation with total urine estimation in 24 hour collection of urine.

Materials and Methods: We conducted a prospective observational study among pregnant women with HTN attending Department of Obstetrics and Gynaecology, Lok Nayak Hospital, Maulana Azad Medical College, New Delhi. Two hundred patients with singleton pregnancy with hypertension and gestational age >20 weeks were included in the study. Both 24-hour urine protein measurement and a spot urine PCR was done for every patient. Follow up was performed till delivery and outcomes were noted.

Results: Significant proteinuria was found in 64 (32%) patients. The study suggested moderate degree of correlation between spot urine PCR and 24 hour urine protein, with a correlation coefficient of 0.47, $p < 0.001$ ($n=200$). The correlation coefficient for ambulatory patients was 0.415 whereas it was much higher i.e. 0.776 for nonambulatory patients.

The ROC curve analysis revealed an excellent sensitivity of 96.3% and specificity of 84.2% with AUC 0.91 (excellent) for a cut-off value of spot PCR >0.19 to detect significant proteinuria in our population. The negative predictive value was 98.4% and positive predictive value was 69.3%.

Conclusion: The spot urine Protein Creatinine ratio can be considered an excellent ruling out test. However, women with abnormally high spot urine PCR should undergo 24-hour urine protein measurement before clinical intervention is done.

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1. Introduction

Hypertensive disorders can cause serious complications in 5-10% of all pregnancies and are recognized as a pertinent cause of maternal morbidity and mortality.^{1,2} Hypertensive disorders of pregnancy result in a high proportion of hospital admissions, labour induction and maternal and fetal morbidity and mortality.

The presence of proteinuria is the cornerstone in the diagnosis of preeclampsia. It develops late in the course of the disease & its presence is a sign of worsening hypertensive disease. Hence, it is essential to diagnose proteinuria accurately.

Estimation of protein in a 24-hour urine collection has been the long-standing way to estimate proteinuria.

The collection of urine for 24 hours is however, time consuming and needs strong co-operation; requires hospitalization, is inconvenient, costly and inaccurate due to incomplete collection and poor compliance. This can result in unnecessary delay of diagnosis and management of preeclampsia.

A need therefore exists, for a rapid, as well as a valid and accurate test to identify significant urinary proteinuria. Measurement of protein-creatinine ratio (PCR) in a spot urine sample, is an alternative method for quantitative evaluation of urine protein. It avoids the influence of variations in urinary protein concentration and provides an additional convenient and speedy technique to do so.

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There is scarceness of information concerning regarding accuracy of spot Urine P/C ratio and its recommended cut-off in Indian population. The actual clinical relevance of urine PCR as a substitution of 24-hour urine protein excretion for detecting significant proteinuria in prelamptic patients still remains unclear. There are some reports with conflicting results, and therefore the variability in cutoff values between studies doesn't enable an even recommendation.

Therefore we undertook this study wherein, we estimated the correlation between spot urine PCR and 24-hour urine protein excretion pregnant patients with high blood pressure to search out out the its validity, and conjointly to see its cut-off in our population

2. Materials and Methods

This study was carried out in pregnant women with hypertension attending the department of Obstetrics and Gynaecology, Lok Nayak Hospital, Maulana Azad Medical College, New Delhi 110002. Eligible Patients were enrolled during November 2014 to April 2016. The study was approved by the ethics council of Maulana Azad Medical College, New Delhi.

2.1. Study design

Prospective Observational study

2.2. Sample size

Two hundred eligible patients were recruited during the course of the study.

2.3. Calculated using

$$N = \frac{4pq}{l^2}$$

Where,

$p=68$ (prevalence of the study variable in the population i.e. proportion of patients with abnormal urine PCR among patients with significant proteinuria, adopted from metaanalysis of previous similar studies)

$$q = (1-p) = 32$$

l = allowable error in the study (recommended as 10%)
= 10% of p (10% of 68=6.8)

$$n = 188$$

Patients with Singleton pregnancy of Gestational age of at least 20 weeks with diagnosed hypertension (using the standard criteria, that is, systolic blood pressure ≥ 140 OR diastolic blood pressure ≥ 90 mmHg or both on two determinations at least 4 hours apart) were included in the study.

Patients with pre-existing renal conditions or significant bacteriuria at the time of collection of sample were excluded from the study. Patients with pregestational diabetes mellitus or connective tissue disorders were also

deemed ineligible for the study.

A detailed general and obstetric history was taken for every enrolled patient. An informed consent was taken from all enrolled patients. Every patient was assessed with respect to general physical, systemic and obstetric examination.

Patients underwent all routine Antenatal investigations (Blood group typing, hemoglobin estimation, Liver function test, Kidney Function Test, Urine routine examination, HIV testing, HBsAg testing, STS). Spot urinary protein creatinine ratio was performed in all patients. Additionally, 24-hour urine protein estimation was carried out in all patients as a gold standard test. Collection of 24-hour urine was begun in the morning after discarding first voided urine of morning. The sample was collected in a clean bottle and patient was told to clean the perineal area with saline before sample collection.

After the last sample and completion of 24-hour urine collection, a single void midstream clean catch sample was taken for PCR estimation

The samples were analysed by autoanalyser in biochemistry lab using BECKMAN COULTER OLYMPUS AU 480.

Patients were managed as per standard protocol in accordance with 24-hour urine protein value. Spot urine PCR ratio was hidden from the treating consultant. Lab performing spot urine P/C ratio was blinded to 24-hour urine protein result.

All the patients were followed up till delivery and pregnancy outcomes were noted.

SPSS 21 software was used for calculations.

Significant proteinuria- 24-hour urine protein >300 mg

Non-ambulatory patient - restricted activity for >24 hour at the time of sample collection.

3. Results

The mean period of gestation was 36.06 ± 2.6 weeks.

The average systolic blood pressure at the time of recruitment was 133.3 ± 6.34 and the mean Diastolic blood pressure at the time of recruitment was 84.3 ± 5.31 . Out of the 200 patients with hypertension, Blood pressure of 196 (98%) was being controlled with antihypertensive drugs.

The mean spot urine PCR was 0.31 ± 1.51 . Only 8 patients (4%) had spot urine PCR greater than 0.5.

The correlation coefficient (r) was found to be 0.47 ($n=200$) which was highly significant with $p < 0.001$. The relationship was nonlinear.

The correlation coefficient for ambulatory patients was 0.415 whereas for non-ambulatory patients, it was much higher i.e. 0.776 with both of the correlations being highly significant. Hence, the calculated correlation coefficient between 24-hour urine protein and spot UPCR was stronger in case of nonambulatory patients.

Receiver operator curve was plotted for spot urine PCR depicting its sensitivity and specificity for predicting

significant proteinuria. The ROC curve is depicted in Figure 1. Area under curve is 0.91 (S.E=0.02) that is considered to be significant.

We found that the highest sensitivity and specificity value for predicting significant proteinuria was obtained corresponding to a cut off for spot urine PCR in our population >0.19. The ROC curve analysis revealed a sensitivity of 96.3% and specificity of 84.2% with AUC 0.91 (excellent) for a cut-off value of spot PCR >0.19 to detect significant proteinuria in our population.

Table 1: Demographic characteristics of study population

Characteristic	
Mean age	26.30 + 3.16 years.
Mean parity	
Mean gestational age	36.06 + 2.6 weeks.
Mean systolic blood pressure	133.3+6.34
Mean diastolic blood pressure	84.3+5.31
Classification of hypertension	Gestational hypertension 145(72.5) Preeclampsia 42(21) Chronic hypertension 8(4) Eclampsia 5 (2.5)
Antenatal care	Booked 189(94.5) Unbooked 11(5.5)

Table 2: Distribution of 24-hour urine protein values

24-hour urine protein (mg)	Number of patients	Percentage
<150	75	37.5%
150-299	61	30.5%
300-999	56	28%
1000-1999	7	3.5%
2000-2999	1	0.5%
>2999	-	-
Total	200	100%

Table 3: Distribution of spot urine protein creatinine ratio (PCR) values

PCR cut off value	Sensitivity	Specificity
0.13	98.1%	67.1%
0.15	79%	78.1%
0.17	96.1%	81.5%
0.19	96.3%	84.2%
0.20	79.6%	8.2%
0.25	53.7%	91.1%
0.30	38.9%	92.5%

4. Discussion

An accurate and rapid quantitation of urinary protein is important in the management of hypertensive disorders in

Table 4: Sensitivity and specificity of urine PCR at various cut off values

Spot urine PCR	24-hour urine protein		
	>300 mg/dl	<300 mg/dl	
Positive (>0.19)	52 (TP)	23 (FP)	75
Negative (<0.19)	2 (FN)	123 (TN)	125
Total	54	146	200

PPV and NPV values for spot urine PCR (protein creatinine ratio)

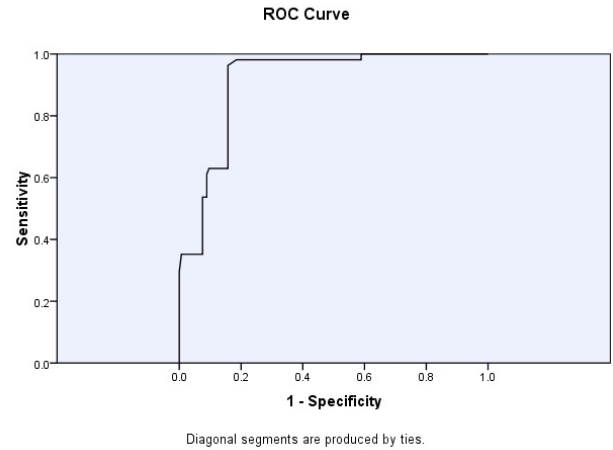


Fig. 1: Showing ROC curve generated for predicting cut off for spot urine PCR for predicting significant proteinuria

pregnancy. This can help us know the severity of proteinuria and the disease process, which can alter the course of management. Several investigators have explored other means of quantifying proteinuria in a shorter period. In this study a comparison of the PCR with the standard 24-hour protein estimation using the various indices of validity was quite revealing. In the present study, 200 pregnant women with hypertension attending a tertiary care hospital were included. The mean age of the patients was 26.30 years and the mean gestational age was 36 weeks. Neithardt et al evaluated 30 patients whose average age was 29.4 years.³ Rodriguez- Thompson DR studied 138 women with median age 30 years.⁴ In Shehzabian et al’s study, 81 pregnant women were included, and their mean age was 26.5 ± 3.6 years.⁵ In the 2008 study by Aggarwal et al., they showed a moderate degree of correlation between spot urine PCR and 24-hour urine.⁶

In our study, we found a correlation coefficient of 0.47, which was highly significant at p<0.001 (n=200). The ROC curve analysis revealed a sensitivity of 96.3% and specificity of 84.2% with Area under curve being 0.91 (considered to be excellent) for a cut-off value of spot PCR >0.19 to detect significant proteinuria in our population. The negative

predictive value was 98.4% and positive predictive value was 69.3% hence proving it to be an excellent ruling out test.

Our results are in agreement with the study done by Nischintha in seventy-five patients which showed a moderate correlation between 24-hour urine protein and spot urine P/C ratio ($r = 0.38$) with a $P = 0.001$. The ROC curve analysis in their study revealed a sensitivity of 73.53% and specificity of 65.85% with AUC 0.80 (good test) for a cut-off value of spot P/C >0.60 to detect significant proteinuria.⁷

Aggarwal et al reported a significant association between the two tests with a correlation coefficient of $r = 0.60$ ($P < 0.01$) that is, a moderate correlation and the sensitivity and specificity of spot urine PCR at a cut-off value >1.14 of 72% and 75%, respectively.

There have been conflicting reports too. Durnwald and Mercer, in their study, reported a poor correlation with a coefficient of 0.41 between 24-hour urine and spot urine PCR. The ROC analysis revealed no clear shoulder although the AUC was 0.80 with a sensitivity of 55.8% and specificity of 81% at a cut-off value of 0.30 for spot urine PCR. The difference of findings between their report and ours may be due to the difference in the study population. The wider exclusion criteria in our population may explain the higher positive and negative predictive values found in our study, as diabetes mellitus and preexisting renal disease may lead to an elevation in urine albumin. Furthermore, Durnwald and Mercer also recruited outpatient participants, who could have incomplete urine collections.⁸

Because of the variability in laboratory methods for measuring proteinuria in different reported studies, several cutoff points and different units for the urinary PCR have been reported, thereby precluding valid comparisons among such studies.

In our present study, the ROC curve analysis revealed a sensitivity of 96.3% and specificity of 84.2% with Area under curve as 0.91 (excellent) for a cut-off value of spot P/C >0.19 to detect significant proteinuria in our population.

The high specificity shown by spot urine PCR in our population signifies that it will accurately diagnose preeclampsia and prevent unnecessary interventions.

Our study had an FPR of 15.7%. False positive reactions may occur due to a plenty of reasons like concentrated urine, high pH, contamination with vaginal discharge. The false positive rate for the spot urine PCR of 15.7% still leaves some room for errors in diagnosis and premature intervention.

The clinician and the patient are more interested to find out what the probability is that a positive result is genuinely positive. This determines the confidence in a particular investigation. The study reveals that for a cutoff of 0.19, the positive predictive value of spot urine PCR was 69.3% and

the negative predictive value was 98.4%. High NPV with a modest PPV means that women with abnormal spot urine PCR should undergo 24-hour urine protein before clinical intervention is done.

This was in agreement with the study by Taherian et al done in 2006, in which it was found that the cutoff value of > 0.18 yields a sensitivity of 86.3% and a specificity of 100%.⁹

In another study by Al et al., done to study the use of Random urine protein-creatinine ratio for predicting proteinuria in new-onset mild hypertension in late pregnancy in 185 women, the recommended cutoff for spot urine PCR to detect significant proteinuria was 0.19 with sensitivity of 85% and specificity of 73%.¹⁰

However, conflicting reports also exist. In a study Chen et al. performed on 60 pregnant women with preeclampsia, level of random UPCR in cutoff points is 0.30.¹¹

Differences in cutoff values could be due to variations in urine sample collections, participant demographics, sample size, inclusion, and exclusion criteria, and other effective factors.

Since the protein excretion is influenced by postural change, being higher in the standing than in supine position, the ambulatory status of the patients was also given importance while interpreting the results. In our study, 88.5%(177) of the patients were ambulatory and non-ambulatory patients constituted 11.5%(23) of the total patients. The correlation coefficient for ambulatory patients was 0.415 whereas it was much higher for nonambulatory patients i.e. 0.776, with both of the correlations being highly significant.

Furthermore, spot urine Protein creatinine ratio estimation can be performed on similar biochemical analyser as the one used for 24-hour urine protein estimation which was the same analyser used for running routine urgent biochemical tests. Hence, it was found to be very cost effective and feasible.

Also, repeating a random sample is much easier and quicker to accomplish.

Our study is one of the larger studies done to study the correlation between 24-hour urine protein and spot urine PCR and find an appropriate cut-off value to detect significant proteinuria in our population till date. By employing appropriate and strict exclusion criteria, we eliminated false high urine protein values.

However, as our data was slightly skewed and did not necessarily represent all age groups equally, there may be some limitations to it. Another limitation was that only one patient had spot urine PCR above 2. So, correlation at very high levels of proteinuria could not be studied.

Therefore, we recommend that the cutoff for spot urine protein creatinine ratio for detecting significant proteinuria in our population should be 0.19. Although spot urine protein creatinine ratio is an excellent test to rule out

preeclampsia, the women with abnormal spot urine PCR should undergo 24-hour urine protein before clinical intervention is done. Further studies in patients with severe proteinuria are needed.

5. Conclusion

In our study, there is a moderate degree of correlation between Spot urine PCR and 24-hour urine protein with r equal to 0.47, $p < 0.001$ ($n=200$). We also found that the best cut-off for spot urine PCR in our population would be 0.19 or greater.

6. Source of Funding

None.

7. Conflict of Interest

None.

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