

# A Comparison of Spot Urine Protein-Creatinine Ratio vs. 24 hours Urinary Protein Excretion in Women with Pre Eclampsia

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**Abstract:** *Objective:* To evaluate diagnostic accuracy of spot urine protein-creatinine ratio for the diagnosis of proteinuria among patients with preeclampsia taking 24 hours urinary protein concentration > 300 mg/24hrs as gold standard.

*Study Design:* This was a cross sectional study.

*Introduction:* Preeclampsia can lead to significant morbidity and mortality. One of the important characteristic of diagnosis of preeclampsia is proteinuria. Gold standard for detection of significant proteinuria among these patients is 24 hours urinary proteins level (>300 milli grams). However, spot urinary protein-creatinine ratio can also detect proteinuria and save patients from botheration for collection of 24 hours urine. Previously, variable sensitivities, specificities and diagnostic accuracy of spot urinary protein-creatinine ratio had been calculated. So, this study was designed to determine diagnostic accuracy of spot urinary protein-creatinine ratio.

*Methods:* 551 patients with preeclampsia were included. All patients had spot urinary protein-creatinine ratio (>0.3 was cutoff for proteinuria). All patients had 24 hours urinary protein test (>300 grams cutoff for proteinuria) as gold standard. Diagnostic accuracy of urinary protein-creatinine ratio was detected by determining sensitivity, specificity and accuracy.

*Results:* Sensitivity, specificity, and accuracy of spot urinary protein-creatinine ratio were 95.8%, 94.2% and 91.6%, respectively.

*Conclusions:* Due to its high sensitivity, specificity and diagnostic accuracy, urinary protein-creatinine ratio is a reliable test for diagnosing proteinuria among patients with preeclampsia.

**Keywords:** Preeclampsia, spot urinary protein-creatinine ratio, 24 hours urinary protein, diagnostic accuracy.

## INTRODUCTION

The origin of preeclampsia have been under investigation for many years though the definitive cause of the disease remains a mystery [1]. Preeclampsia is defined as the development of hypertension, proteinuria or both after 20 weeks of gestation in a women with previously normal blood pressure [2]. It is a common cause of maternal morbidity, occurs in up to 2-8% of all pregnancies [3].

Pregnancy by it's vary nature is an altered state of the body's ordinary workings. In a normal pregnancy, coagulation is already elevated and there is a marked reduction of about 50% in the velocity of venous blood flow in the legs by as early as 25 weeks of pregnancy [4]. This reduced blood flow persists until about six weeks after childbirth [4]. The hypertension and proteinuria seen in preeclampsia are outward signals indicating many internal alterations to the systems of the body. When examined closely, the effects of preeclampsia on the body are far reaching and warrant further analysis [5].

Preeclampsia is often thought of as a disorder with two components, an abnormal placental implantation coupled with endothelial dysfunction complicated by other maternal factors [6,7]. The reality is much more complex. There are changes seen in the renal and vascular systems overall. Due to endothelial dysfunction, the factors that allow blood vessel development behave in an altered manner resulting in vasoconstrictors and procoagulants being released into the blood vessels of the placenta [8]. Endothelial lesions are seen in the kidneys along with scores of microscopic thromboses which result in reduced renal function [9]. Even more telling is the reduced kidney function that is present in nearly half of the cases of preeclampsia before proteinuria even manifests [6]. Confounding factors such as preexisting disease states also have an effect. Diseases like diabetes, autoimmune disorders and preexisting hypertension amplify preeclampsia risks [4]. Most recently, pre-eclampsia and related pregnancy induced hypertensive disorders have been categorized as a risk factor for future cardiovascular disease while at the same time the number of pregnancy related deaths due to cardiovascular dysfunction has been rising [8,9].

The diagnosis of preeclampsia is determined by the presence of elevated blood pressure and significant proteinuria ( $\geq 300$  mg per 24 h) after the 20th week of

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gestation [10]. The gold standard for measuring proteinuria is the 24-h urine collection [11]. Unfortunately, the 24-h urine collection takes an entire day to collect and is, therefore, not available to guide clinical decisions upon first evaluation. This can delay the diagnosis and hence treatment [12]. A rapid screening test to predict 24-h proteinuria, in combination with other presenting signs and symptoms, can help a clinician determine the appropriate amount of surveillance and guide care during the initial 24-h period [13].

An alternative method for quantitative evaluation of proteinuria is the measurement of protein-Creatinine ratio in a spot urine sample, which provides a more convenient & rapid method to assess protein excretion. But clinical utility of urine protein-Creatinine ratio as a substitute of 24-hour urinary protein excretion is still unclear [14].

According to the National Kidney Foundation KDOQI Guidelines, proteinuria can be accurately assessed by the use of the urine protein-to-creatinine ratio (U pr:cr) [15]. The ratio is determined by dividing the urine protein (mg/dl) by the urine creatinine (mg/dl). The numerical outcome of the ratio is roughly equal to the 24hr protein excretion in g/day per 1.73m<sup>2</sup> body surface area [16]. The validity and reliability of this method has been validated in diabetic [17] and nondiabetic nephropathy [18].

In a study by Leañós-Miranda A, *et al.*, [19] it was determined that sensitivity of protein:creatinine ratio (at a value of > 0.3) as an indicator of protein excretion  $\geq 300$  mg/24 h was 98.2% and 98.8%, respectively. Positive and negative predictive values were 97.2% and 99.2%, respectively, and positive and negative likelihood ratios were 79.2 and 0.02, respectively. They considered it a reliable test.

In a study by Dwyer *et al.*, [12] the sensitivity of urinary protein-creatinine ratio for detection of proteinuria was (at a value of > 0.3) 66% and a specificity of 95%. So, they determined it as unreliable test.

In a study by Eslamina L, *et al.*, [20] for protein creatinine ratio best predicted significant proteinuria with sensitivity of 87.9% specificity of 92.6%, positive and negative predictive values of 90.6% and 89.3% respectively.

Keeping in mind the differences of sensitivity and specificity of both studies, the reliability of this test

stays unclear. This highlights the need for further studies to determine the diagnostic accuracy of this test. This will help us in making future strategies in assessment of proteinuria among our patients with preeclampsia.

## OBJECTIVE

The objective of this study was to evaluate the diagnostic accuracy of spot urine protein-creatinine ratio for the diagnosis of proteinuria among patients with pre-eclampsia taking 24 hours urine protein count > 300 mg/24hrs as gold standard.

## OPERATIONAL DEFINITION

### Pre-Eclampsia

It was defined as systolic blood pressure of 140mmHg or higher & diastolic blood pressure 90mmHg or higher taken 04 hours apart, with proteinuria (>300mg) after 20th week of gestation.

### Significant Proteinuria

It was defined as protein excretion of 300mg or more in 24-hours period. It was labeled positive if value is > 300mg/24 hrs.

### Protein-Creatinine (P/C) Ratio

It was defined as urine proteins in mg divided by urine Creatinine in mg in spot urine sample. It was taken as positive if value is > 0.30.

### Diagnostic Accuracy

It was assessed by calculating sensitivity, specificity, positive predictive value and negative predictive value.

The presence of proteinuria was detected by spot urinary protein creatinine ratio (> 0.3) and confirmed on 24 hours urinary protein level of > 300mg/24hrs (gold standard). (Labeled as positive or negative).

## MATERIAL AND METHODS

### Sample Size

With the expected sensitivity = 87.9%

Specificity = 92.6%

Expected prevalence = 8%

Desired precision = 1

Confidence interval = 95%

The calculated sample size was 551 cases.

### Sample Technique

Non probability consecutive sampling.

### Sample Selection

#### Inclusion Criteria

- Patients with preeclampsia (as per operational definition)
- Singleton pregnancy
- Proteinuria of 1+, 2+ and 3+ (by dipstick test)

#### Exclusion Criteria

1. Patients with chronic hypertension (BP > 120/80 mm of Hg)
2. Known intrinsic kidney disease (creatinine > 1.0)
3. Patients on heavy exercise
4. Bacteriuria (pus cells > 5 on urine C/E)
5. Bed rest longer than 24hrs
6. Gestational diabetes (BSR > 180 mg/dL)
7. Molar pregnancy (On USG)
8. Patients with other systemic illness (evidence on previous medical record)

### Data Collection Procedure

Five hundred and fifty one patients fulfilling the inclusion criteria were enrolled from out patient Department of Obstetrics and Gynecology, Sheikh Zayed Medical College/ Hospital, Rahim yar khan. The Demographic data (age) and detailed history was taken. Previous medical record was checked. Then informed consent was taken. Spot urinary protein creatinine ratio was performed at the Pathology Department by taking urine sample. A ratio of > 0.3 was labeled as proteinuria. The patients were then being asked to collect urine for 24 hours for detection of protein concentration. A concentration of > 300 mg/24hrs was labeled as positive for proteinuria, which was taken as gold standard. All this information was entered on Performa.

### Data Analysis Procedure

Data was analyzed using SPSS version 11. The quantitative variables i.e. age, gestational age, were presented as mean and standard deviation. The qualitative variables i.e. parity and presence or absence of proteinuria (on both spot protein-creatinine ratio and 24 hours urinary proteins level) were presented by calculating frequency and percentages. Diagnostic accuracy, Sensitivity, specificity, positive predictive value and negative predictive value of spot urinary protein/creatinine ratio as diagnostic marker of proteinuria was calculated by generating 2x2 contingency table. Diagnostic accuracy =  $\frac{TP + TN}{TP+TN+FP+FN} \times 100$ .

## RESULTS

### Distribution of Patients by Age

In the study, the mean age of the patients was 26.83 + 9.32 years (range 18 – 43). There were 148 (26.9%) patients of age  $\leq$  20 years, 289 (52.4%) patients of age range of 21 – 30 years, 108 (19.6 %) patients of age range of 31 – 40 years, 6 (1.1%) patients of age range of 41 – 50 years and 0 (0 %) patients of age > 50 years (Table 1).

**Table 1: Distribution of Patients by Age (n=551)**

Age in years	No. of patients	Percentage
$\leq$ 20	148	26.9
21 – 30	289	52.4
31 – 40	108	19.6
41 – 50	6	1.1
> 50	0	0
Mean $\pm$ SD	26.83 $\pm$ 9.32	

### Distribution of Patients by Parity

In the study, 356 (64.6%) patients were primigravida, 162 (29.4%) patients were multigravida and 33 (6%) patients were grand multigravida (Figure 1).

### Distribution of Patients by Gestational Age

In the study, there were 26 (5%) patients with gestational age 21 – 25 weeks, 147 (27%) patients with gestational age 26 – 30 weeks, 182 (33%) patients with gestational age 31 – 35 weeks, and 196 (35%) patients with gestational age of 35 – 38 weeks (Table 2).

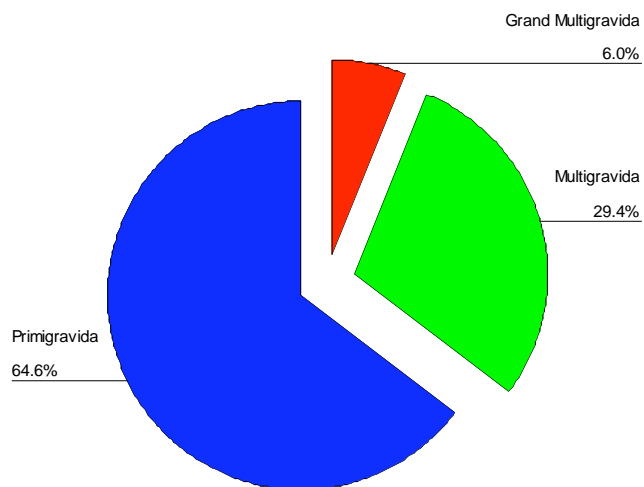


Figure 1: Distribution of patients by Parity (n=551).

Table 2: Distribution of Patients by Gestational Age (n=551)

Gestational age (weeks)	No. of patients	Percentage
21 – 25	26	5
26 – 30	147	27
31 – 35	182	33
35 – 38	196	35

**Comparison of Spot Urinary Protein/Creatinine Ratio vs. 24 Hours Urinary Protein Level**

Out of 551 patients included in the study, the spot urinary protein/creatinine ratio was detected to be positive in 435 patients. Of these, 429 were proved on 24 hours urinary proteins level, so were labeled as true positive, while rest of the ten patients were labeled as false positive. Spot urinary protein/creatinine ratio was negative in total 116 patients. Out of these 19 were positive on 24 hours urinary protein level (false positive) and 97 were also seen negative on 24 hours urinary protein level (true negative) (Table 3).

Table 3: Comparison of Spot Urine Protein-Creatinine Ratio with 24 Hours Urinary Protein Ratio (n=551)

Spot urinary protein/creatinine ratio	24 hours urinary protein level (300mg/dL) (Gold Standard)		Total
	Positive (>300mg/dL)	Negative (<300mg/dL)	
(>3) Positive	429 (TP)	6 (FP)	435
(<3) Negative	19 (FN)	97 (TN)	116
Total	448	103	551

**Diagnostic Accuracy of Spot Urinary Protein/Creatinine Ratio for Diagnosis of Proteinuria among Patients with Pre-Eclampsia**

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of spot urinary protein/creatinine ratio for diagnosis of proteinuria among patients with preeclampsia was 95.8%, 94.2%, 98.6%, 83.6% and 95.4%, respectively (Table 4).

Table 4: The Diagnostic Accuracy of Spot Urine Protein-Creatinine Ratio

	Sensitivity rate = 95.8%
	Specificity rate = 94.2%
Predictive value of	
	Positive test = 98.6%
Predictive value of	
	Negative test = 83.6%
	Accuracy = 95.4%

**DISCUSSION**

Pre-eclampsia is a significant contributor to maternal mortality. Concerns typically arise when patients present with increased blood pressure. One of the ways to diagnose pre-eclampsia, apart from the blood pressure criteria, is to look for the presence of significant proteinuria. The gold standard for proteinuria, a key component in the assessment of pre-eclampsia, is a 24-hour urinary protein excretion, which is cumbersome both for the patients and the staff handling the urine collection, and subject to error due to inaccurate timing and/or incompleteness.

This is one of the studies with a large sample size of 551 patients, which was performed to determine the diagnostic accuracy of the spot urinary protein/creatinine ratio for diagnosis of proteinuria and the results of this study showed a high diagnostic accuracy of the test i.e. 95.4%.

In literature, there are many other clinical trials which have described the diagnostic accuracy of the spot urinary protein/creatinine ratio for detection of proteinuria among patients with pre-eclampsia. The mean age of the patients in our study was 26.83 + 9.32 years. The mean age of total patients observed in study of Sharma A, et al. was 25.151+3.77 years. Islamian L [20], documented that mean age of the patients was 30.6 years. The majority of the patients (79.3%) in our study were of young age group of < 30 years. This observation is similar to that of study by Sharma A, et al., [22] who observed that 87.92% patients were of age group 21 - 30 years in their study.

In our study, 64.6% patients were primigravida. Sharma A, *et al.* [22] also observed that approximately, 46.03% patients in their study were primigravida.

In our study, approximately 68% patients were seen in gestational age of 31 – 40 weeks. In study by Sharma A, *et al.*, [22] it was observed that majority of subjects (42.06%) with pre-eclampsia belonged in group 28 - 32 weeks gestational age [22].

In our study, the diagnostic accuracy of the spot urinary/creatinine ratio was high i.e. 98.6%. The study also yielded a high sensitivity and specificity i.e. 95.8% and 94.2%, respectively. The positive predictive value was also high (98.6%).

In literature, there are many other clinical trials in this regard, with different cut off values. Different studies had documented variable results, depending upon the cut off values.

In a study by Leanos-Miranda *et al.*, [19] the sensitivity of the urinary protein/creatinine ratio was 98.2 %, specificity was 98.8 %, PPV and NPV were 99.2% and 97.2%. Like our study, they showed a very high sensitivity of the test at a cut off value of 0.3.

However, Durnwald *et al.*, [21] did not show a high sensitivity or specificity. They found that test had a less sensitivity of 72.6% and less specificity of 73%. They also documented a low PPV and NPV of 45.2% and 89.7%. However, the cut off value in their study was > 0.3, which was a bit higher than our study.

Shahbazian N, *et al.*, [23] found the strong correlation between the spot P/C ratio and 24 hr urine protein excretion ( $r = 0.84$ ,  $P < 0.001$ ). The optimal spot P/C ratio cut off point was 0.2 for 300mg/ 24hr of protein excretion, with a sensitivity, specificity, positive predictive value and negative predictive value of 91.2%, 87.8%, 94.4% and 96.8% respectively.

In study by Sharma A, *et al.*, [22] the maximum sensitivity 99.1% was found with protein creatinine ratio cut off point 0.14 and maximum specificity 100% was found with protein creatinine ratio cut off point 0.37 i.e. >0.3).

Several cut-off and different units have been reported for PCR value in different reported studies. Some reported optimal cut-off points (0.15-0.5mg/mg) [23]. In our study, a cut off value of > 0.3 has shown that it is highly sensitive and specific and yields a very high diagnostic accuracy.

In our study, we observed a high frequency of patients who were positive for proteinuria. There were

448 (81.3%) patients who were positive for proteinuria. This is due to the reason that ours is a tertiary care unit and we included pre-eclamptic population with high blood pressure (systolic > 140mm of Hg and diastolic > 90mm of Hg).

We had only 19 (3.4%) patients who were false negative, so chances of missing the patients with diagnosis of proteinuria was very low.

The only drawback in our study was that we admitted the patients for collection of the urine, which caused some extra burden to hospital in terms of bed occupancy. Otherwise, getting a true sample of 24hrs urinary proteins might have been difficult.

## CONCLUSION

This study concludes that spot urinary protein/creatinine ratio has shown a high sensitivity, specificity and diagnostic accuracy (at a cut off value >0.3). So, it can be considered a reliable investigation among pre-eclamptic patients. The spot urine protein creatinine ratio can provide excellent discrimination between patients with and without significant proteinuria. This test can be used for prompt clinical decision in spite of waiting for 24hr urine collection.

## ABBREVIATIONS

NPV = Negative predictive value

PCR = Protein creatinine ratio

PPV = Positive predictive value

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Received on 27-10-2014

Accepted on 10-11-2014

Published on 15-12-2014

DOI: <http://dx.doi.org/10.14205/2309-4400.2014.02.02.1>© 2014 Khan *et al.*; Licensee Pharma Publisher.

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