Journal of Advanced Medical and Dental Sciences Research
@Society of Scientific Research and Studies

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr ICV 2018= 82.06 UGC approved journal no. 63854

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Original Research

A Prospectively comparative study to evaluate urine protein/creatinine ratio in Hypertensive disorders of Pregnancy as an alternative to 24 hour method

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***ABSTRACT*:**
Background: Proteinuria is a major component of preeclampsia. Urine protein measurement after 24-hour urine collection is the traditional standard method for the detection of proteinuria. It is time-consuming. As an alternative, random spot sampling for a urine protein to creatinine (P/C) ratio has been investigated. **Objectives:** To prospectively compare random urine protein/creatinine ratio in Hypertensive disorders of Pregnancy. **Methods:** A prospective study was carried on all patients admitted with suspected / Diagnosed Hypertensive disorders of Pregnancy in Northern Railways Central Hospital, between May 2008 to June 2009 . After 24 hour urine for Protein evaluation, a random sample for Protein/creatinine ratio was taken from all patients.Urine protein was measured by Biuret Method and urine creatinine by Jaffey's method . Significant Proteinuria was taken as $\geq$ 300 mg/ 24 hours by 24 hour method and $\geq$ 0.3 mg/mg by Protein/creatinine ratio. Both 24 hour protein and protein/creatinine ratio were compared using statistical analysis 24 hour protein was taken as gold standard for comparison. **Results:** 90 patients were enrolled in the study. Out of 90 patients , 30 patients had significant proteinuria. Mean Age of the study group was 25 years .53.3 % of patients were nullipara. Mean value of 24 hour protein was 0.477 g/day and mean value of protein-creatinine ratio was 0.489 mg/mg. The random protein-reatinine ratio showed a good correlation with 24 hour protein with a 90 % sensitivity and a specificity of 86.67 %. The False Positive rate and the Negative Positive rate of random protein-creatinine ratio was 13.33 % and 10 % respectively. **Conclusion:** Protein-creatinine ratio can emerge as a good alternative to 24 hour protein in proteinuria evaluation.
Key words: Protein/creatinine ratio, proteinuria, pre-eclampsia.

Received: 18 November 2018 Revised: 12 February 2019 Accepted: 14 February 2019

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This article may be cited as: Kaur J. A Prospectively comparative study to evaluate urine protein/creatinine ratio in Hypertensive disorders of Pregnancy as an alternative to 24 hour method. J Adv Med Dent Scie Res 2019;7(4):133-137.

INTRODUCTION:

Hypertensive disorders are the most common medical complications of pregnancy with an incidence of 12-22% and are rampant globally. They are the leading and most dreaded cause of both maternal and fetal morbidity and mortality. Because proteinuria is required for the diagnosis of preeclampsia, and it is also a criterion for identifying disease severity, measurement of proteinuria in pregnant women with hypertension is important.[1-3] Significant proteinuria is defined by the International Society for the Study of Hypertension in Pregnancy as excretion of ≥300 mg of protein in a 24-h urine specimen. Thus, the gold standard for diagnosis of significant proteinuria is based on a 24-h urine collection.[2,3]

Measurements of the protein:creatinine ratio in a single urine specimen may be a reliable and quick test to estimate 24-h protein excretion in a nonpregnant population because the ratio of 2 stable excretion rates (creatinine and protein) minimizes the time involved, thus providing a faster estimate of 24-h protein excretion. The clinical utility of the relationship between the gold standard for detecting significant proteinuria and the urine protein:creatinine ratio in hypertensive pregnant women still remains unclear. Although several studies have shown that the urine protein:creatinine ratio is a predictor of significant

proteinuria, others have found a weaker value of this test for this purpose. Nevertheless, the appropriateness of the urine protein:creatinine ratio as a screening test for proteinuria is still unclear, in part because of the paucity of large studies on proteinuria in pregnant women with hypertension.[3-6]

So, this prospective study was designed to compare random urine protein/creatinine ratio in Hypertensive disorders of Pregnancy.

MATERIALS AND METHOD:

A prospective study was carried on 90 patients admitted with suspected / Diagnosed Hypertensive disorders of Pregnancy in Northern Railways Central Hospital over the period of 12 months. After 24 hour urine for Protein evaluation, a random sample for Protein/creatinine ratio was taken from all patients.

Preeclampsia was described by a blood pressure of 140/90 mmHg or higher after 20 weeks of gestation accompanied by new-onset significant proteinuria, which is accepted as urine protein excretion greater than or equal to 300 mg/24 h. Women with overt diabetes, chronic hypertension, preexisting chronic renal disease, or urinary tract infections were removed from the study.

All patients were on moderate bed rest during the 24-hour urine collection, which started on the morning following the hospitalization. Spot mid-stream urine specimens for measuring P/C ratio were obtained shortly before the 24-hour urine collection was begun. First urine in the mornings was not taken. Women who identified bacteria on urine microscopy or who were on more than 24 hours' bed rest, due to the potential effect of postural proteinuria on spot urine-protein excretion, were excluded. All patients had intact membranes. Urinary protein was determined by the Biuret method. Urine creatinine level was measured by a modified Jaffe test

Significant Proteinuria was taken as $\geq$ 300 mg/ 24 hours by 24 hour method and $\geq$ 0.3 mg/mg by Protein/creatinine ratio. Both 24 hour protein and protein/creatinine ratio were compared using statistical analysis 24 hour protein was taken as gold standard for comparison .

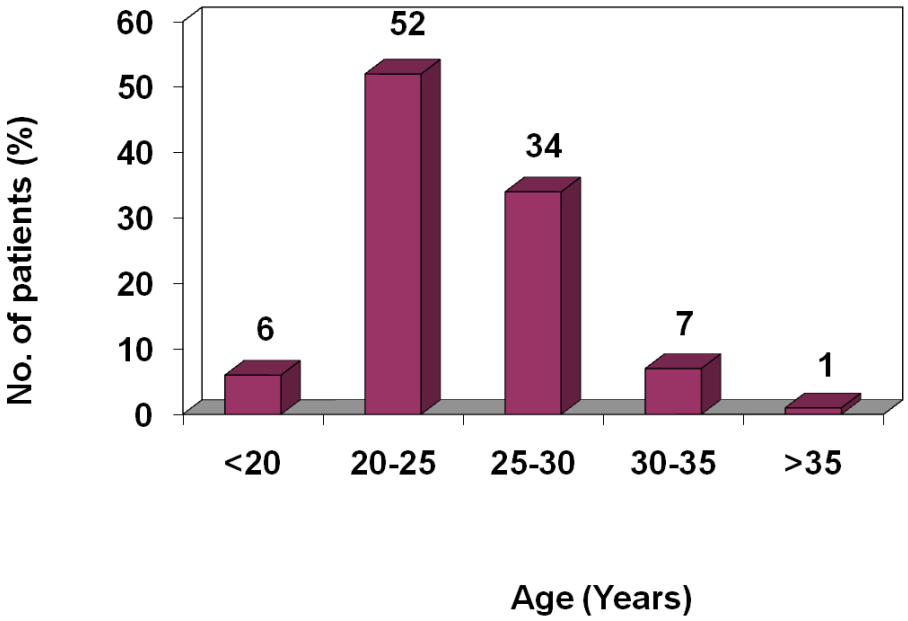
The correlation between the P/C ratio in the spot urine samples and urinary protein excretion in the 24-hour collections were evaluated using the Spearman correlation test. Using protein values of 300, 1.000, 2.000, 4.000, and 5.000 mg on 24-hour urine collections, the performance of the protein-creatinine ratios to predict proteinuria was analyzed

The Statistical Package for the Social Sciences (SPSS Inc., version 17; Chicago, IL, USA) was used for statistical analyses.

RESULTS:

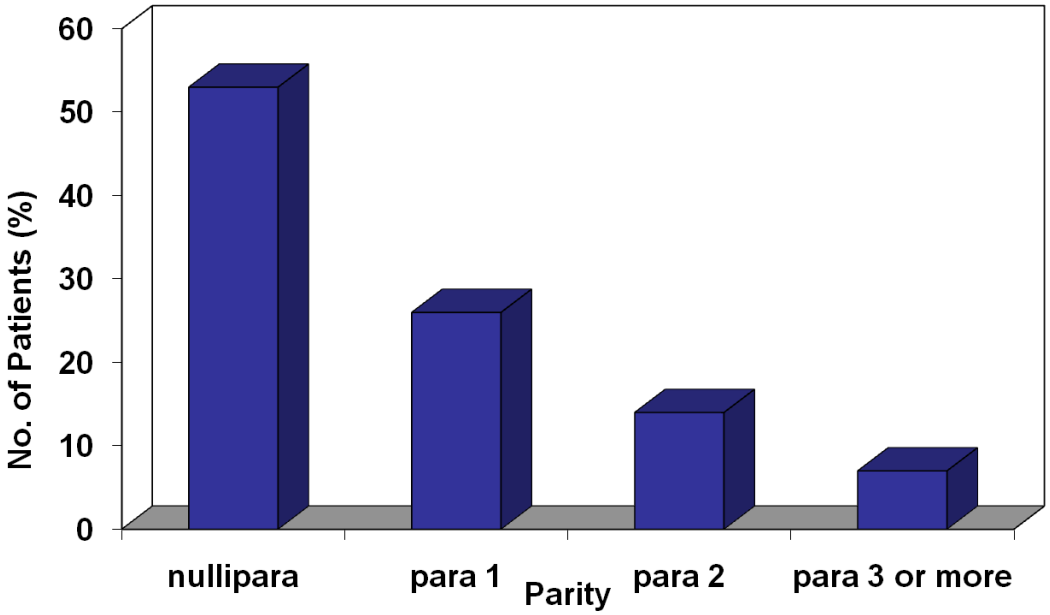
Total 90 patients were enrolled in present study. Thirty patients had significant proteinuria. The median maternal age was 25 years ranging from 19- 37 years. (Graph 1)

Graph 1: Age Distribution of Patients

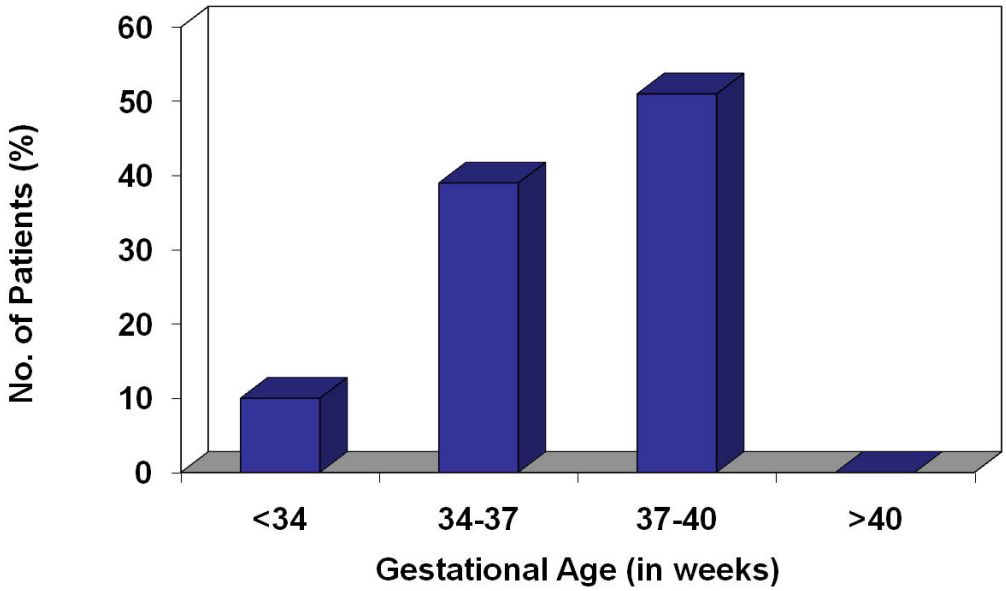


Graph 2 showed that 53.3 % of patients were nullipara , only 10 % patients were < 34 weeks and None of the patients were postdated.

Graph 2: Parity of Patients



Graph 3: Gestational Age of Patients



Graph 3 revealed that majority patients were in 37-40 weeks gestation.

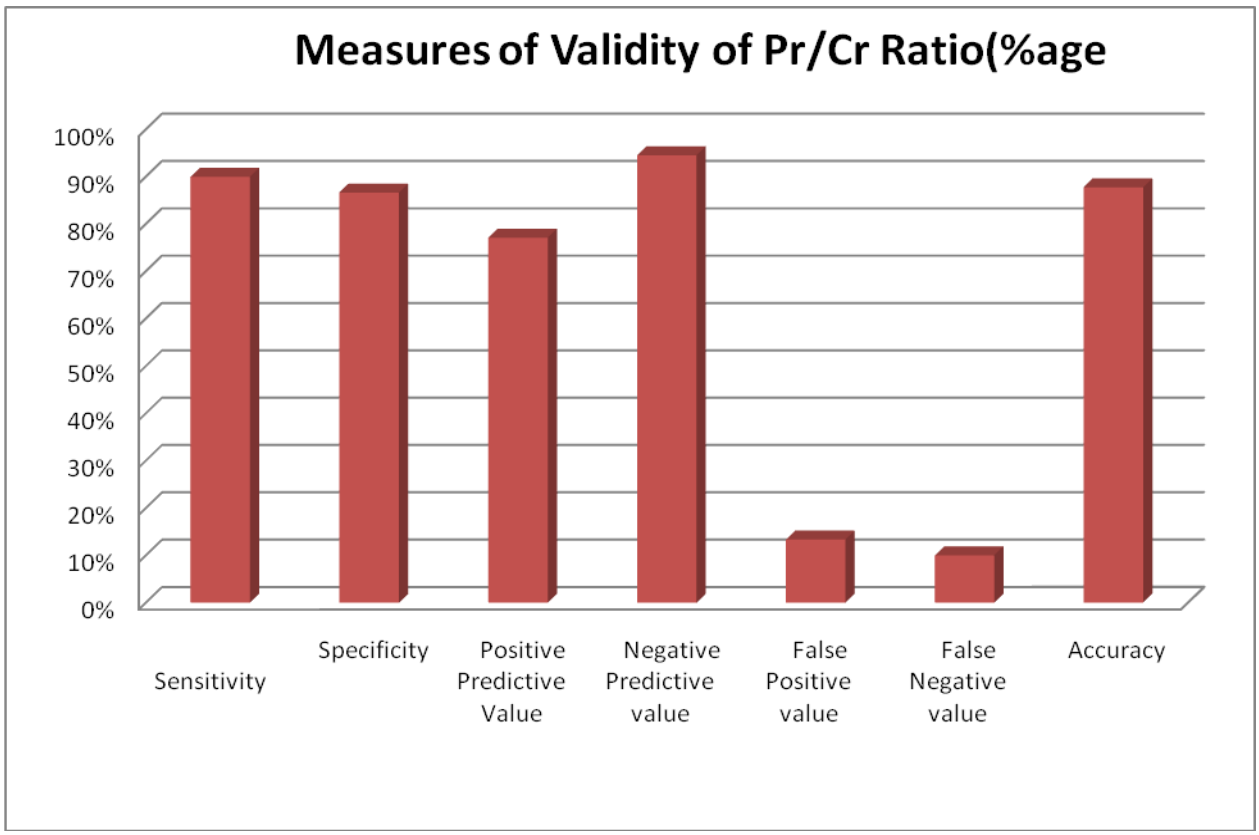
Table 1: Measures of validity of Protein creatinine ratio

Sensitivity	**90 %**
Specificity	86.67%
False Positive rate	13.33 %
False Negative rate	10 %
Accuracy	87.78 %

Table 2: Clinical variables of pre-eclamptic population

IUGR	**40 (19%)**
Blood urea nitrogen (mg/dL)	10.2±3.6
Serum creatinine (mg/dL)	0.54±0.2
<1	200
≥1	11
Uric acid (mg/dL)	5.2±1.4
Total protein (g/dL)	6.0±0.8
Albumin (g/dL)	3.6±0.6
Spot urine protein (mg/dL)	254.6±15.5
Spot urine creatinine (mg/dL)	82.8±4.5
Urinary protein (mg/24h)	2801.8±20.8
Protein/creatinine ratio (mg/mg)	3.0±1.2

Graph 4: Measures of Validity of Pr/Cr Ratio (%age)



DISCUSSION:

Testing for proteinuria is very important in the treatment of preeclampsia. It is mandatory in evaluating women with hypertensive disorders of pregnancy, and is necessary to establish the diagnosis of preeclampsia, as well as its severity. Urinary protein excretion during a 24-h period, however, is considered to be cumbersome and subject to error due to inadequate collection. In assessing a diagnostic test, the following considerations are important: [7,5,6]

(a) the gold standard should provide the closest approximation to the true status of the disorder under study; (b) the clinical spectrum of the disease under study (including individuals with low prior probability to have the disorder); (c) the necessity of making blind measurements; and

(d) the optimal cut off point taken to lower at maximum both false-positive and false-negative results.

All of these are fundamental to determine the diagnostic performance of an assay.

Due to high accuracy, reproducibility, and convenience compared with 24-hour protein collection, the P/C ratio in spot urine was developed as an alternative test in the non-pregnant population. Morales et al. reported the potential error in determining protein in a spot urine sample due to daily variation that does not exceed the error in collecting a 24-hour urine sample. Also, until now, the majority of studies evaluating spot urine P/C ratio in pregnant women with suspected preeclampsia have been found to be closely correlated with the 24-hour urine protein measurement. However, in pregnant women, there is no reliable evidence about the optimal cut-off value for spot urine P/C ratio for defining preeclampsia. The most recent meta-analysis implied that the optimum threshold for P/C ratio to define significant proteinuria is between 0.30 and 0.35, regarding to sensitivity and specificity values above 75%; when the sensitivity and specificity above 80% was accepted, there was no cut-off found.[3-6]

The sensitivity was 90% and specificity 86.67% in our study. Similar results were found by Alfredo Leanos Miranda et al[8]. with a cutoff of 0.19 or greater, Rodriguez-Thompson and Lieberman reported a sensitivity of 91% and a specificity of 70%.15 Durnwald and Mercer[10] reported a sensitivity of 91% and specificity of 48% with a cutoff point of 0.20. 16 Using Bayes' theorem, given a prior probability of 21% for significant proteinuria, a negative predictive value of 97% was estimated from the study of Rodriguez- Thompson[9] and 95% from that of Durnwald and Mercer.[10]

Xiong X, Mayes D et al.[4] In their study on impact of pregnancy induced hypertension on fetal growth found that after adjustment for duration of gestation and other confounders, preeclampsia and severe preeclampsia increased the risk of intrauterine growth restriction and low birth Weight Similar findings were observed by, Ivanov S, Sfiokova et al.[11] The method of detection of proteinuria with random protein creatinine ratio is faster and within safe limits to aid diagnosis and in early start of treatment hence ensuring better fetomaternal outcome. Also many studies have stressed on early detection and prompt management of patients with proteinuria that is beneficial for patient and fetus. The random protein-creatinine ratio can be used in serial testing with 24-hour urine collection in mild hypertensive disorders of pregnancy. For a patient with a positive random urinary protein to creatinine ratio, proceeding with collection of a 24-hours urine sample seems a reasonable option.

CONCLUSION:

Arandom urine protein:creatinine ratio measurement provides a good estimation of total 24-h proteinuria in hospitalized pregnant women and can replace the time-consuming 24-h urine collection. Further studies are needed for standardization of the method and cut off to be used for Protein creatinine ratio.

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