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A Two-hour Urinary Protein-creatinine Ratio for Predicting Significant Proteinuria in Preeclampsia

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ABSTRACT

Objective: To determine an optimal cutoff level of urinary protein-creatinine ratio (PCR) obtaining from 2 hours urine collection from women admitted with suspected preeclampsia for predicting significant proteinuria.

Study design: Diagnostic test.

Subject: Pregnant women with gestational age ≥ 20 weeks who were admitted at Bangkok Metropolitan Administration Medical College and Vajira Hospital for evaluation of preeclampsia were studied prospectively. They were instructed to collect a 24-hour urine in two separate containers: one for the first 2 hours urine and the other for the following 22 hours urine specimens. Each sample was measured for volume, protein, and creatinine values. The first 2-hour urinary PCR and total 24-hour proteinuria were calculated. A receiver operating characteristic curve (ROC) of the 2-hour urinary PCR was constructed in order to determine the optimal cutoff level for estimate the degree of proteinuria.

Results: A total of 182 out of 187 women completed the study; 137 (75%) had significant proteinuria. This study demonstrated moderate correlation between 2-hour urine protein and 24-hour urine protein(r=0.451). By using a 2-hour urinary PCR, the optimal cutoff level to predict significant proteinuria was ≥ 0.30 which yielded sensitivity, specificity, PPV, NPV and area under the ROC curve of 71.5%, 71.1%, 88.3%, 45.1% and 0.801 respectively. On the other hand, a cutoff level of ≥ 0.05 had a sensitivity of 100%, while the cutoff level of ≥ 2.0 offered 100% specificity.

Conclusions: The 2-hour urinary PCR is not a good test to predict significant proteinuria due to its high false negative rate.

Keywords: preeclampsia, significant proteinuria, urinary protein-creatinine ratio

Introduction

Preeclampsia affects 5-10% of all pregnancies and is one of the leading causes of maternal and fetal/neonatal morbidity and mortality.[1,2] Typically, it is manifested after 20 weeks of gestation; the diagnosis is made by the presence of hypertension in combination with

significant proteinuria.[1,2] In clinical practice, identification of the disease in its early stages would be helpful since an intensified monitoring, treatment, or delivery could be provided before life-threatening complications occur.

In addition to establishing the diagnosis, urine protein analysis is essential for the classification of severity of preeclampsia, i.e. mild or severe degree. Either single-voided urine sample or 24-hour urine collection is used for the determination of proteinuria. The latter is considered to be the gold standard; [1,2] however, this approach is inconvenient in that it requires sometimes hospitalization and good cooperation of the pregnant women in collecting urine samples. Besides, its time-consuming process could lead to a delayed diagnosis, which might result in delayed treatment or even poor pregnancy outcomes.

Aside from the 24-hour urine collection, the urinary dipstick, which is a method of assessing protein in single-voided urine samples, is commonly used in an obstetric practice.[1] This approach yields advantages in terms of rapidity and convenience. However, many studies found that the test is a poor predictor of 24-hour proteinuria because it detect only urine protein concentration, not a total amount of its excretion.[3-7] The random urinary protein-creatinine ratio (PCR) has been proposed as a more reliable method to evaluate the quantity of proteinuria.[8-11] This was based on the rationale that the PCR might represent variability in urine protein and creatinine excretion throughout the day.[8-10] Nevertheless, some authors found that the diagnostic performance of this technique was still influenced by the diurnal variations of protein and creatinine.[11,12] It is also questionable that the sample obtained immediately when a woman arrives at the clinic would be reliable, since ambulation is recognized as a contributing factor to increased protein excretion.[13]

It is not known whether an intermediate periodic duration of urine collection (i.e. 2-hour, 4-hour, or 6-hour interval) may improve the accuracy of PCR for the evaluation of proteinuria, given time for bed rest and quantifying urine. The aim of this study was to determine the optimal cutoff level of PCR from 2-hour urine collection and to evaluate its diagnostic performance for significant proteinuria (≥ 300mg on 24 hour urine collection) in women with suspected preeclampsia.

Materials and Methods

This study obtained approval from the Bangkok Metropolitan Administration Ethics Committee for Researches Involving Human Subjects. All consecutive pregnant women with gestational age (GA) of ≥ 20 weeks and resting blood pressure ≥ 140/90 mmHg (after laying down for at least 15 minutes), who were admitted to the obstetric ward at our institution between May 2007 and January 2009 for evaluation of preeclampsia were recruited. Exclusion criteria were the pregnant women who had clinical of urinary tract infection, history of renal disease, overt diabetes, chronic hypertension, or incomplete collection of urine sample (a 24-hour urine sample which contained creatinine amount less than 10 mg/kg of body weight).[12]

After hospitalization, the patients were advised to have bed rest. Each of the eligible women was informed about the study and signed consent form. All participants were instructed to collect their urine in two, clean separate containers. The first container was for the first 2-hours of urine while the second one was for the remaining 22-hour urine sample. Total collection time was 24 hours. Each container was refrigerated at 2-8°C in the refrigerator for urine preservation. All women who were diagnosed with mild or severe preeclampsia were treated according to the clinical practice guidelines of the department.

Laboratory tests were done at the clinical pathology laboratory of the institution. Urinary protein quantification was determined by the biuret reaction using the automated colorimetric method model Olympus AU series (E For L Inc., Tokyo, Japan). Urinary creatinine was determined by the modified Jaffé reaction (E For L Inc., Tokyo, Japan) using the autoanalyzer Olympus AU series. The Randox control (Randox Laboratory Inc., UK) was used to calibrate the machine each morning for a daily quality assurance. The first 2-hour urinary PCR was calculated by dividing whole amount of protein (mg) by whole amount of

creatinine (mg), in the first 2-hour urine collection. The total 24-hour urinary volume, protein, and creatinine were calculated by summation of the 2-hour and 22-hour urine volume, protein, and creatinine respectively. A 24-hour urine sample which contained creatinine amount less than 10 mg/kg of body weight was considered inadequate urine collection.[12]

Sample size was calculated based on a pilot study of 20 pregnant women. With the maximum allowable error (d) of 10% and α = 0.05, total of 173 subjects were needed. We added up 5% of samples in the event that the enrolled subjects met any of the exclusion criteria, accordingly the study required 182 subjects.

Data collection included: maternal age, parity, body mass index (BMI), highest systolic and diastolic blood pressures, serum creatinine and uric acid levels, gestational age (GA) at- and method of urine collection, total 24-hour urinary protein and creatinine, and 2-hour urinary PCR. Body mass index (BMI) was calculated from the height and weight measured on admission. We calculated GA based on the last menstrual period or ultrasound examination whatever was corresponse with clinical findings.

Statistical analysis was performed with the SPSS software package version 11.5 (SPSS Inc., Chicago, IL, USA). The STATA 7.0 (Stata Corp., College station, TX, USA) was additionally used to generate confidence interval (CI). Baseline characteristics were presented as mean with standard deviation (SD) or median with range as appropriate for continuous variables, and as number with percentage for categorical variables. The Student t-test or Mann-Whitney U test were used to compare continuous variables, and χ^2 test was used to compare categorical variables. P-value of < 0.05 was considered statistically significant. Based on the 24-hour proteinuria of ≥ 300 mg as the gold standard for diagnosing significant proteinuria in preeclampsia,[14] the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with associated 95% CIs of the first 2-hour urinary PCR at various cutoff levels were calculated. A receiver operating characteristic (ROC) curve was constructed and evaluated for the area under the curve (AUC) to find the apropriate cutoff level to predict significant proteinuria.

Results

One hundred and eighty two out of 187 women (97.3%) had completed the 24-hour urine collection during the study period. Their mean age (± SD) was 28.4± 6.8 years; 114 (62.6%) were nulliparous. Mean gestational age on admission was 35.9 ± 4.2 weeks. Details of characteristics and laboratory data of the study population are presented in Table 1.

One hundred and thirty seven out of one hundred and eighty seven (75%) had significant proteinuria (≥ 300 mg) on 24 hour urine collection while the remaining (25%) had insignificant proteinuria (< 300 mg). The median (range) of significant and insignificant proteinuria were 1,149.0 (308.5-50,052.6) mg. and 187.4 (61.0-288.0) mg, respectively. Amongst the 137 women who had significant proteinuria in 24 hour urine protein collection, 27 (14.8%) had protein excretion between ≥ 2 and <5 g and 15 (8.2%) had protein excretion ≥ 5 g.

The relationship between 2-hour urinary PCR and 24-hour proteinuria is shown in Fig. 1, with a moderate correlation coefficient of 0.451 ($p < 0.001$). When including only the patients whose total urinary protein amounts were in range of ≥ 300 mg to ≤ 2 g, the correlation was still moderate ($r = 0.484$; $p < 0.001$)

The ROC curve of 2-hour urinary PCR to predict significant proteinuria is presented in Fig. 2. As shown in Table 2, a cutoff level of ≥ 0.05 yielded a sensitivity of 100% but poor specificity of 2.2 %, while a ratio of ≥ 2.0 yielded a specificity of 100% and sensitivity of 32.1%.

At the cutoff level of ≥ 0.30, revealed the sensitivity, specificity, PPV, and NPV of 71.5%, 71.1%, 88.3%, and 45.1% respectively with the AUC of 0.801 (95% CI 0.74-0.87; $p < 0.05$). At this cutoff level,we found false negative rate of 28.5% comprising of mild preeclampsia patients who deliveried without any complication. So the cutoff level of ≥ 0.30 was selected as the most appropriate.

Aside from significant proteinuria, we further determined if any cutoff value of the 2-hour urinary

PCR could predict severe proteinuria (24-hour urine protein ≥ 2 g). We found that at a high cutoff point of ≥ 12.0, the results showed 100% specificity and 100% PPV. At this cutoff point, 15 women (8.2%) would gain advantage in terms of early treatment for severe preeclampsia.

Table 1. Characteristics of the study population (n = 182)

Characteristics	Proteinuria		P-value
	Significant (≥ 300 mg)	Insignificant (< 300 mg)	
	(n = 137)	(n = 45)	
Age (years), mean (SD)	28.3 (7.1)	28.5 (6.3)	0.83 [a]
Nullipara, n (%)	89(65)	25(55.6)	0.26 [b]
BMI (kg/m^2), mean (SD)	31.1 (6.1)	29.7 (5.9)	0.17 [a]
Systolic blood pressure (mmHg), mean (SD)	162.7 (22.2)	152.5 (17.0)	< 0.01*, [a]
Diastolic blood pressure (mmHg), mean (SD)	106.8 (15.1)	101.9 (11.2)	0.045*, [a]
Serum creatinine (mg/dl), mean (SD)	0.8 (0.2)	0.7 (0.1)	0.01*, [a]
Serum uric acid (mg/dl), mean (SD)	6.2 (1.7)	5.4 (1.3)	< 0.01*, [a]
GA at urine collection (weeks), mean (SD)	36.1 (4.2)	35.7 (4.2)	0.56 [a]
24-hour urine protein (mg), median (range)	1,149.0 (308.5-50,052.6)	187.4 (61.0-288.0)	< 0.01*, [c]
24-hour urine creatinine (mg), median (range)	1034.0 (711.0-2,825.0)	946.4 (719.9-2,805.0)	0.50 [c]
2-hour PCR, median (range)	0.76 (0.05-32.4)	0.19 (0.03-1.95)	< 0.01*, [c]

BMI = body mass index; GA = gestational age; PCR = protein-creatinine ratio;
SD = standard deviation. *P < 0.05 = significant
[a] Student T-test ; [b] χ^2 test; [c] Mann-Whitney U test

Table 2. Accuracy of protein-creatinine ratio at difference cutoff level for predicting of significant proteinuria

cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 0.05	100.0	2.2	75.7	100.0
≥ 0.20	83.2	51.1	83.8	50.0
≥ 0.30	71.5	71.1	88.3	45.1
≥ 2.00	32.1	100.0	100.0	32.6

PPV = positive predictive value; NPV = negative predictive value

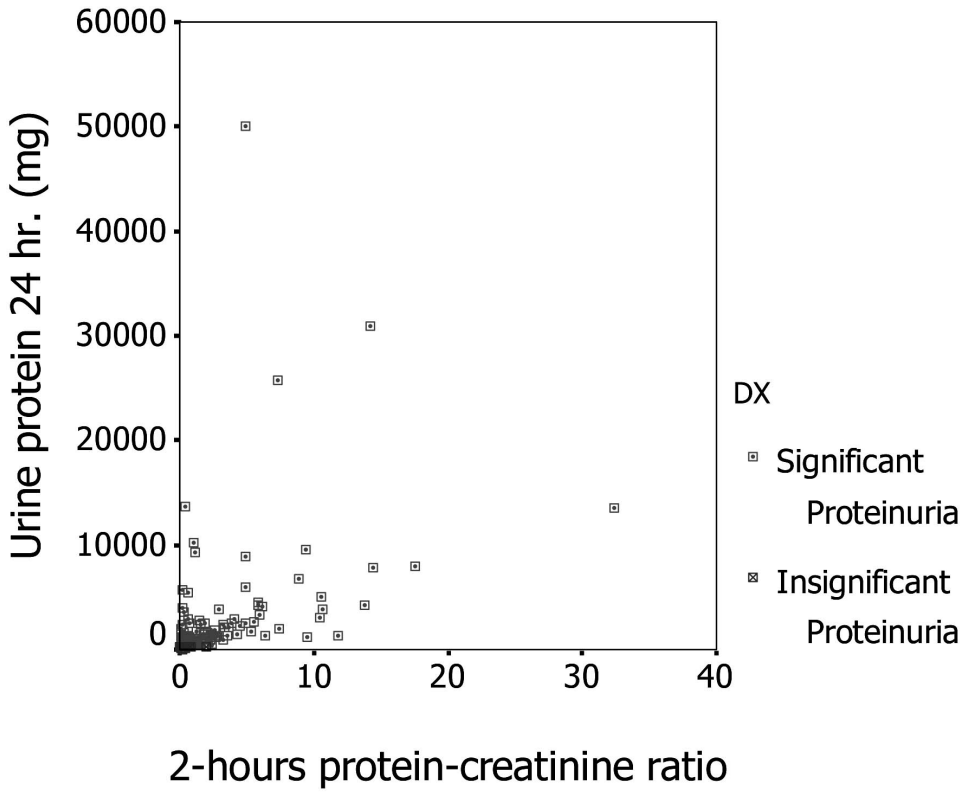

Fig. 1. The relationship between 2-hour urinary protein-creatinine ratio and 24-hour proteinuria ($r = 0.451$; $p < 0.001$)

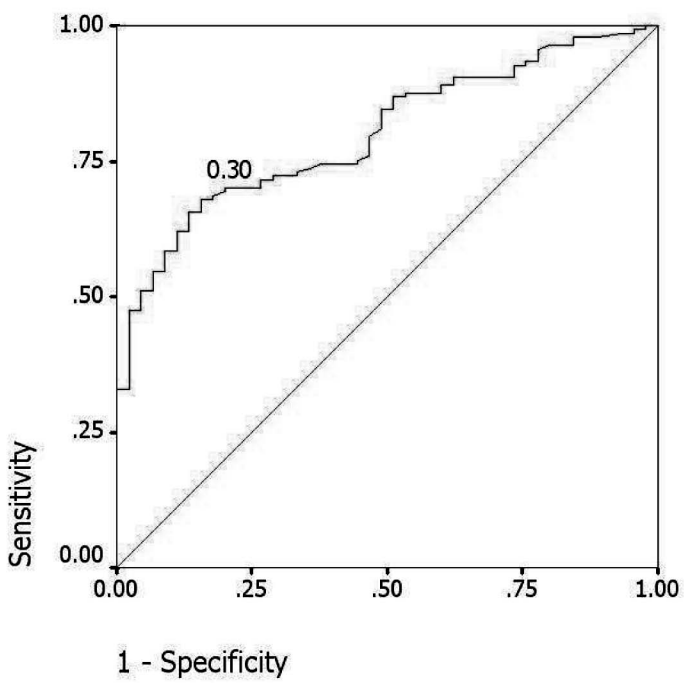

Fig. 2. The receiver operating characteristic curve of 2-hour urinary protein-creatinine ratio for predicting significant proteinuria (at cutoff level 0.30, AUC = 0.801; 95% CI 0.74-0.87)

Discussion

The presence of significant proteinuria is one of the criteria to diagnose preeclampsia. The 24-hour urine protein measurement has been employed for the diagnosis of proteinuria during the past decades, and is still used as the gold standard at present. However, some questions regarding the test exist: will the patients be convenient in collecting urine? Will the amount of urine collection be accurate since it takes a long period of time? In addition, a longer time in urine collection may result in a delayed diagnosis leading to delayed treatment as well as poor pregnancy outcomes.

Due to the disadvantages of 24-hour urine protein measurement, several investigators have attempted to establish an alternative approach that consumed less time in urine protein collection. One previous study demonstrated that the PCR in random urine samples had a good correlation with the 24-hour total protein excretion in pregnant women with urine protein > 1g.[13] In contrast, another study found that when urine protein was > 2g, there was a poor correlation between the PCR and 24-hour total protein amount, and therefore the PCR could not replace the 24-hour urine protein measurement to identify mild to severe pre-eclampsia in significant proteinuria.[15] Likewise, it appeared that using PCR in random urine might be limited by the influence of the diurnal variations of protein and creatinine.[11,12]

In addition to the random PCR, Tara et al[16] found that measurement of 2-hour urine protein excretion yielded a high sensitivity of 77.8% and specificity of 87.5% for the evaluation of significant proteinuria as compared to the gold-standard 24-hour urine protein collection. However, in their study, the sample size was limited to only 26 patients and it is questionable for its accuracy since urine protein excretion throughout the day is inconsistent with diurnal variation. Thus, we decided to use 2-hour urine PCR instead of urine protein collection in a 2 hour-period. We expected to gain more accuracy in the diagnosis by using creatinine as the denominator to adjust the diurnal variation effect of urine protein excretion at different time. Our study, with more sample size of 182 women, revealed a significant correlation of first 2-hour urinary protein-creatinine ratio with conventional 24-hour urine protein collection. Furthermore, we found that the optimal cutoff point of ≥ 0.30 yielded a high PPV of 88.3%. Nevertheless, due to its high false negative rate of 28.5%, we therefore could not recommend it as an alternative method to the 24-hour urine protein measurement.

Aside from looking for the advantage or accuracy of the 2-hour PCR to rule in the women for further investigation of significant proteinuria, we also explored the data to determine whether our proposed test could be used to rule in or rule out the patients for a condition of severe proteinuria. We found that all women with the 2- hour PCR exceeding 12.0 had severe protenuria. Thus, this might yield a benefit in selecting the women for prompt treatment of severe preeclampsia, i.e. receiving magnesium sulfate therapy or delivery. Nevertheless, this 12.0 cutoff point was rather high, so only small percentage of women (8.2% in our study) would gain benefit.

In conclusion, our results demonstrated that the 2-hour PCR was not a good test to predict significant proteinuria. However, this test could predict severe proteinuria and therefore could be use for a rapid diagnosis of severe preeclampsia, particularly when decisions of termination of pregnancy have to be made.

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อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะจากการเก็บปัสสาวะที่ 2 ชั่วโมงเพื่อวิเคราะห์ระดับโปรตีนในปัสสาวะที่มีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ

ศุภชัย เรืองแก้วมณี, ชาดากานต์ ผโลประการ, สุมนมาลย์ มนัสศิริวิทยา, บุษบา วิริยะสิริเวช

วัตถุประสงค์ *: เพื่อหาอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่เหมาะสมที่สุดจากการเก็บปัสสาวะที่ 2 ชั่วโมง ในการวิเคราะห์ระดับโปรตีนในปัสสาวะที่มีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ*

รูปแบบการวิจัย *: การวิจัยแบบการตรวจเพื่อวินิจฉัยโรค (Diagnostic test) จำนวน 182 ราย*

วิธีดำเนินการวิจัย *: สตรีที่มีภาวะความดันโลหิตสูงขณะตั้งครรภ์ และอายุครรภ์มากกว่า 20 สัปดาห์ที่เข้ารับการรักษาแบบผู้ป่วยในที่วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล สำนักการแพทย์ กรุงเทพมหานคร จะได้รับการเก็บปัสสาวะใน 2 ชั่วโมงแรกและอีก 22 ชั่วโมงถัดมา เพื่อหาปริมาณปัสสาวะ ปริมาณโปรตีนและปริมาณครีเอทินีน นำมาคำนวณเป็นค่าของอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 2 ชั่วโมงและหาปริมาณโปรตีนในปัสสาวะ 24 ชั่วโมงตามลำดับ จากนั้นนำไปทดสอบทางสถิติหาค่าอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 2 ชั่วโมง ที่เหมาะสมที่สุดในการวินิจฉัยภาวะมีโปรตีนในปัสสาวะอย่างมีนัยสำคัญ (≥ 300 กรัมใน 24 ชั่วโมง)*

ผลการวิจัย *: จากผู้ป่วย 182 รายจากทั้งหมด 187 ราย มีข้อมูลครบถ้วน; พบว่า 137 ราย (ร้อยละ 75) พบว่ามีความสัมพันธ์ปานกลางระหว่างโปรตีนในปัสสาวะที่ 2 ชม. และ 24 ชม. (r=0.451) มีโปรตีนในปัสสาวะอย่างมีนัยสำคัญร้อยละ 75 พบว่าอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 2 ชั่วโมงที่เหมาะสมที่สุดในการวินิจฉัยผู้ป่วยครรภ์เป็นพิษคือ 0.30 โดยมีค่าความไวร้อยละ 71.5 ความจำเพาะร้อยละ 71.1 ค่าพยากรณ์ผลบวกร้อยละ 88.3 ค่าพยากรณ์ผลลบร้อยละ 45.1 นอกจากนี้ค่าที่มากกว่า 2.0 ขึ้นไปมีค่าความจำเพาะร้อยละ 100 และค่าที่น้อยกว่า 0.05 ความไวร้อยละ 100*

สรุป *: อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะ 2 ชั่วโมงแรกไม่ใช่การที่ทดสอบที่เหมาะสมในการวิเคราะห์ระดับโปรตีนในปัสสาวะที่มีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ เนื่องจากอัตราผลลบลวงสูง*