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Spot Urine Albumin to Creatinine Ratio versus Urine Protein to Creatinine Ratio for the Diagnosis of Proteinuria in Pregnancy

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ABSTRACT

Objectives: To evaluate the correlation of the spot urine albumin to creatinine ratio (UACR) and the urine protein to creatinine ratio (UPCR) with 24-hour urine protein (UP-24) collection and to explore the diagnostic performances of these parameters for detecting significant proteinuria in pregnancy

Materials and Methods: This cross-sectional study was conducted on pregnant women at gestational ages 20-41 weeks who had clinically suspected proteinuria and were prospectively enrolled from November 2015 to April 2016. Random urine samples for UACR, UPCR and 24-hour urine collection for protein and creatinine were examined.

Results: A total of 115 pregnant women were evaluated. Using UP-24 as the reference standard, significant proteinuria was identified in 39 cases (33.9%). UACR had a higher level of correlation than UPCR with UP-24 (r = 0.884 and 0.834, respectively). The areas under the receiver characteristics curves (ROC-AUC) of UACR and UPCR were 96.6% (95%CI; 93.8-99.9) and 94.5% (95%CI; 90.4-98.6), respectively. The diagnostic threshold of UACR for significant proteinuria was 42 mg/g. (94.9% sensitivity and 86.8% specificity), whereas the UPCR cutoff value was 0.26, (87.2% sensitivity and 90.8% specificity). Predicted UP-24 using spot UACR adjusted by maternal age had the highest ROC-AUC of 97.4% (95%CI; 95.1-99.6), with a sensitivity of 94.9% and a specificity of 90.8%.

Conclusion: Spot UACR showed better correlation with UP-24 than UPCR. Spot UACR adjusted for maternal age, yielded a good diagnostic performance that was not associated with the time of urine collection and underlying diseases.

Keywords: preeclampsia, urine albumin to creatinine ratio, urine protein to creatinine ratio, proteinuria.

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อัตราส่วนอัลบูมินต่อครีอะตินีนกับอัตราส่วนโปรตีนต่อครีอะตินีนในปัสสาวะ สำหรับวินิจฉัยการรั่วของโปรตีนในปัสสาวะระหว่างการตั้งครรภ์

ปรุฬห์ สนุ่นรัตน์, ณัฐฐิณี ศรีสันติโรจน์, มรุต ญาณารณพ

บทคัดย่อ

วัตถุประสงค์: *เพื่อประเมินความสัมพันธ์ของอัตราส่วนอัลบูมินต่อครีอะตินีน (UACR) และอัตราส่วนโปรตีนต่อครีอะตินีน (UPCR) จากการเก็บปัสสาวะหนึ่งครั้ง กับโปรตีนในปัสสาวะ 24 ชั่วโมง และเพื่อแสดงการวินิจฉัยของพารามิเตอร์เหล่านี้สำหรับการตรวจสอบการรั่วของโปรตีนในปัสสาวะที่มีนัยสำคัญระหว่างการตั้งครรภ์*

วัสดุและวิธีการ: *การศึกษานี้ได้ดำเนินการในสตรีตั้งครรภ์ อายุครรภ์ 20-41 สัปดาห์ ที่สงสัยว่ามีการรั่วของโปรตีนในปัสสาวะ ตั้งแต่เดือนพฤศจิกายน 2558 ถึงเดือนเมษายน 2559 โดยการเก็บตัวอย่างปัสสาวะแบบสุ่มสำหรับตรวจอัลบูมินต่อครีอะตินีน โปรตีนต่อครีอะตินีน และการเก็บปัสสาวะ 24 ชั่วโมง เพื่อตรวจหาระดับโปรตีนและครีอะตินีน*

ผลการศึกษา: *สตรีตั้งครรภ์ทั้งหมด 115 ราย มีการรั่วของโปรตีนในปัสสาวะที่มีนัยสำคัญมี จำนวน 39 ราย (ร้อยละ 33.9) โดยใช้โปรตีนในปัสสาวะ 24 ชั่วโมง เป็นมาตรฐานอ้างอิง เมื่อเปรียบเทียบความสัมพันธ์กับโปรตีนในปัสสาวะ 24 ชั่วโมง อัตราส่วนอัลบูมินต่อครีอะตินีนมีค่าความสัมพันธ์สูงกว่าอัตราส่วนโปรตีนต่อครีอะตินีน (r = 0.884 และ 0.834 ตามลำดับ) วิเคราะห์โดย Receiver operating characteristic curve พบว่าพื้นที่ใต้กราฟของ UACR และ UPCR คือ 96.6 (ค่าความเชื่อมั่นร้อยละ 95 เท่ากับ 93.8-99.9) และ 94.5 (ค่าความเชื่อมั่นร้อยละ 95 เท่ากับ 90.4-98.6) ตามลำดับ เกณฑ์การวินิจฉัยของ UACR สำหรับการรั่วโปรตีนที่มีนัยสำคัญในปัสสาวะคือ 42 มิลลิกรัม / กรัม (ค่าความไว ร้อยละ 94.9 และค่าความจำเพาะ ร้อยละ 86.8) ในขณะที่เกณฑ์วินิจฉัยของ UPCR เท่ากับ 0.26 (ค่าความไว ร้อยละ 87.2 และค่าความจำเพาะ ร้อยละ 90.8) เมื่อทำนายปริมาณการรั่วของโปรตีนในปัสสาวะ 24 ชั่วโมง โดยปรับค่า UACR ด้วยอายุสตรีตั้งครรภ์ได้ค่าพื้นที่ใต้กราฟมากที่สุด คือ ร้อยละ 97.4 (ค่าความเชื่อมั่นร้อยละ 95 เท่ากับ 95.1-99.6) โดยมีความไวร้อยละ 94.9 และความจำเพาะ ร้อยละ 90.8%*

สรุป: *อัตราส่วนอัลบูมินต่อครีอะตินีนมีความสัมพันธ์กับปริมาณโปรตีนในปัสสาวะ 24 ชั่วโมง สูงกว่าอัตราส่วนโปรตีนต่อครีอะตินีน และเมื่อปรับค่าอัตราส่วนอัลบูมินต่อครีอะตินีนด้วยอายุสตรีตั้งครรภ์ให้ประสิทธิภาพการวินิจฉัยดีที่สุด โดยไม่เกี่ยวข้อง กับช่วงเวลาในการเก็บปัสสาวะและโรคประจำตัวของสตรีตั้งครรภ์*

คำสำคัญ: *ครรภ์เป็นพิษ, อัตราส่วนอัลบูมินต่อครีอะตินินในปัสสาวะ, อัตราส่วนโปรตีนต่อครีอะตินินในปัสสาวะ, โปรตีนรั่วในปัสสาวะ*

Introduction

In normal pregnancy, proteinuria is considered abnormal when the protein content exceeds 300 mg in a 24-hour urine protein (UP-24) collection[1] and is one of the most important criteria used in the differential diagnosis of gestational hypertension and preeclampsia. The quantitation of proteinuria is used to assess the severity of other primary and secondary renal diseases in pregnancy, such as those caused by diabetes mellitus or systemic lupus erythematosus. Moreover, the new onset of proteinuria is used to discriminate superimposed preeclampsia. Hence, the reliable measurement of proteinuria during pregnancy is critical for the accurate diagnosis and management in pregnant women.

Although UP-24 is the key reference for the diagnosis of preeclampsia[2-5], delayed diagnosis and inaccurate results from incomplete urine collection are frequently encountered[6]. A spot urine protein collection is an alternative option. Conventionally, a urine dipstick is widely used because it is inexpensive and easy. However, this technique is inaccurate and has a coarse scale for monitoring[7]. Given the disadvantages of urine dipsticks and UP-24, the urine protein to creatinine ratio (UPCR) is a new method that exhibits better diagnostic accuracy and is currently used to estimate urinary protein excretion instead of UP-24. UPCR is a quantitative method with higher sensitivity and specificity than the urine dipstick[8]. Several studies have reported that UPCR and UP-24 are strongly correlated[9-12] and that a cut-off value of ≥ 0.30 provides the best accuracy[13]. The American College of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG) recommend the use of the urine dipstick only if other quantitative methods are not available[2, 3].

Using the urine albumin to creatinine ratio (UACR) to estimate proteinuria is well established in non-pregnant women for the management of chronic kidney disease[14] and diabetic kidney disease[15] and to predict poor outcomes in diabetic nephropathy with high sensitivity and specificity[16, 17]. However, the evidence supporting the use of UACR in pregnant women is currently limited[3, 5, 18]. A few studies have reported a strong correlation between UACR and UP-24 in pregnant women and have suggested using UACR instead of UP-24[19, 20]. The Society of Obstetricians and Gynecologists of Canada (SOGC) accepted a UACR of 30 mg/g or more as a criterion for the diagnosis of significant proteinuria[5].

The glomerular damage in preeclampsia women has resulted from high blood pressure. Albuminuria reveals increased glomerular endothelial permeability, it is a good indicator of glomerular dysfunction and reflect endothelial permeability better than total protein excretion. In the preeclampsia women who have significant proteinuria but absence the significant albuminuria might have a better prognosis and be less severe symptom[21]. Other urinary-excreted protein such as Tamm-Horsfall glucoproteins and immunoglobulins is present in healthy pregnant women and do not change the level following glomerular damage[20].

The main purpose of this study was to evaluate the diagnostic performance of UACR and UPCR for detecting significant proteinuria during pregnancy. We hypothesize that a robust correlation exists between UACR and UPCR and UP-24. Furthermore, we hope to provide better evidence that UACR could be another reliable method for detecting proteinuria during pregnancy.

Materials and Methods

After approval from the institutional review board of Rajavithi Hospital (Reference number 173/2558, Issue on November 2nd, 2015), this cross-sectional study was conducted in pregnant women over 18 years of age and between gestational ages of 20 to 41 weeks. The indications for measuring proteinuria in these participants included new onset of hypertension (blood pressure > 140/90), suspected preeclampsia, superimposed preeclampsia, or assessment for underlying renal diseases from November 2015 to April 2016. All participants provided written informed consent prior to study inclusion. The exclusion criteria

were indications for emergency termination of pregnancy (including fetal distress, eclampsia or urgent delivery with severe preeclampsia), amniotic membrane rupture, urinary tract infection and vaginitis.

Urine samples were collected in two periods. The first sample was a random spot urine sample (mid-stream urine) to measure urine albumin (mg/L), protein (mg/dL), and creatinine (mg/dL). UACR (mg/g) was calculated using the following formula: (urine albumin/urine creatinine) × 100. UPCR was calculated using the following formula: urine protein/ urine creatinine. The second collection took place over 24 hours to measure urine volume (mL), creatinine (g/24 hr) and protein (g/24 hr). All participants were admitted and provided information on correct urine collection for single and 24-hour samples. The 24-hour urine samples were stored at 4°C. All spot urine and complete 24-hour urine samples were sent to the biochemistry laboratory and processed immediately. Maternal age, body weight before pregnancy, height, gravidity, parity, gestational age, blood pressure at enrollment, maternal underlying diseases, time of spot urine sample collection and starting time of 24-hour urine collection were recorded.

All urine samples were analyzed using the COBAS®8000 C502 automatic analyzer (Roche Diagnostic, Thailand) according to the manufacturer's instructions. Urine protein and urine albumin were measured using turbidimetric assays and urine creatinine was measured using an enzymatic assay. All tests were controlled for precision using within-run and between-run coefficients of variation (CV, %), as follows: protein, 1% (standard < 4%); creatinine, 2.3% (standard < 6%); and albumin, 2% (standard < 4%). Urine creatinine excretion values below 0.6 g/24 hour were considered insufficient and excluded from this study[18].

The sample size was calculated by the following formula

$$n = \frac{z^2_{1-\frac{\alpha}{2}} p(1-p)}{d^2}$$

UACR sensitivity of 0.824 from Huang's Study[19] as a proportion (p) and maximum tolerated error (d) of 0.1 were used for calculation. A total sample size was two - time of the calculated sample size (total n = 112 cases).

Statistical analysis was performed using STATA version 14 (StataCorp, College Station, TX, USA). The baseline characteristics of participants were described using frequencies and percentages for categorical data; the mean, standard deviation, median and range were used for continuous data. UP-24, UACR, and UPCR were initially transformed into a logarithmic scale given the wide range and non-normal distribution of data points. Correlations between UACR or UPCR and UP-24 were calculated using the Pearson correlation coefficient (r). Twenty-four-hour urine protein values of ≥ 300 mg were used as a reference standard for diagnosing significant proteinuria. The receiver operating characteristic (ROC) curves were plotted, and the areas under the curves (AUCs) were calculated. Optimal cutoff values were determined using the Youden index, and the sensitivity, specificity and predictive values were estimated. A multiple linear regression analysis was performed to determine the significant predictive factors for UP-24, and the predictive model was developed based on a linear equation. Model fitting was performed using a backward elimination method based on maximal likelihood estimation. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 137 participants were prospectively enrolled, and 22 of these were excluded (fourteen inadequate collections, five emergency caesarean sections due to fetal distress or non-reassuring fetal heart rate patterns, and three amniotic membrane ruptures). Therefore, 115 women were included in the final analysis. Using UP-24 as a reference standard, significant proteinuria was identified in 39 cases (33.9%). The baseline characteristics of the study population are summarized in Table 1. The

mean age of participants was 32 years (SD, 6.4), and mean gestational age was 31.2 weeks (SD, 5.5). Thirty percent of participants had diabetes mellitus, and 25.2% had chronic hypertension.

The correlation of UP-24 with UACR and UPCR is presented in Fig. 1. Both UACR and UPCR showed strongly significant correlations with UP-24. However, UACR had a higher level of correlation than UPCR with UP-24 ($r = 0.884$ vs. 0.834; $p < 0.001$). There was also a strong level of correlation between UACR and UPCR ($r = 0.90$; $p < 0.001$).

Table 1. Baseline clinical characteristics of the study population.

Baseline characteristic	n = 115
Age (years), mean (SD)	32.0 (6.4)
BMI (kg/m2), mean (SD)	28.0 (6.7)
Gestational age (weeks), mean (SD)	31.2 (5.5)
Parity n, (%)	
Nulliparity	59 (51.3)
Multiparity	56 (48.7)
Underlying diseases n, (%)	
No underlying disease	53 (46.1)
Diabetes mellitus	35 (30.4)
Chronic hypertension	29 (25.2)
Systemic lupus erythematosus	6 (5.2)
Kidney disease	2 (1.7)
Multiple pregnancy	2 (1.7)
Blood pressure	
Systolic blood pressure (mmHg), mean (SD)	150.3 (13.6)
Diastolic blood pressure (mmHg), mean (SD)	93.0 (10.9)
Normotensive* blood pressure n, (%)	12.0 (10.4)
Hypertensive** blood pressure n, (%)	103.0 (89.6)
Laboratory investigation	
24-hour urine protein (mg), median (range)	177 (47-8221)
24-hour creatinine (g), median (range)	0.98 (0.60-2.10)
24-hour urine volume (ml), median (range)	1,700 (1,000-3,780)
Spot UACR (mg/g), median (range)	21.09 (0.94-217,140.00)
Spot UPCR, median (range)	0.19 (0.05-536.00)

BMI, body mass index; mmHg, millimeters of mercury; SD, standard deviation; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio.

* mean arterial blood pressure more than 65 mmHg with both systolic and diastolic blood pressure less than 140 and 90 mmHg at enrollment.

** systolic and/or diastolic blood pressure more than or equal of 140 and 90 mmHg at enrollment.

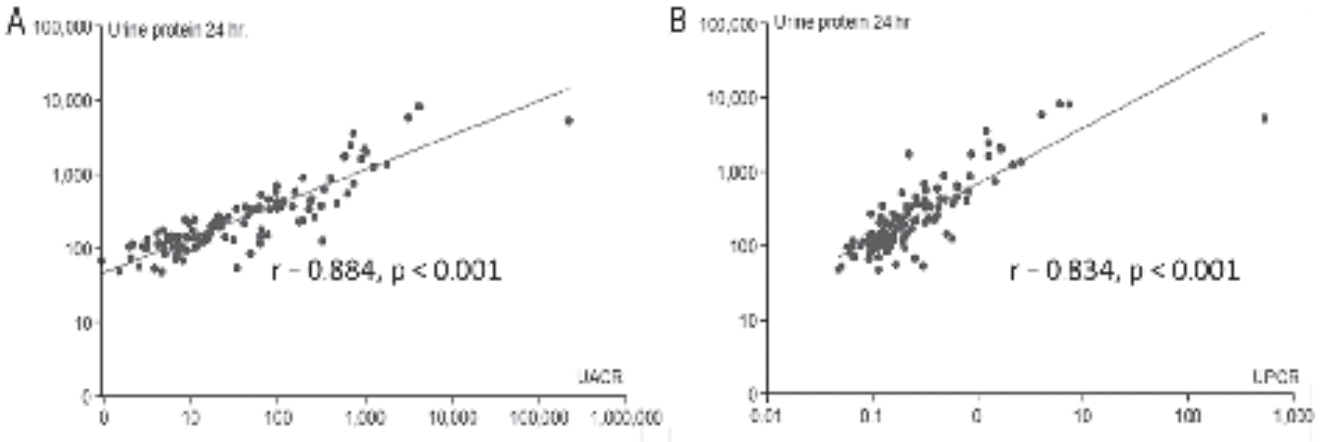

Fig. 1. Correlation of 24-hour urine protein and spot urine albumin to creatinine ratio (A) and spot urine protein to creatinine ratio (B). (r=correlation coefficient)

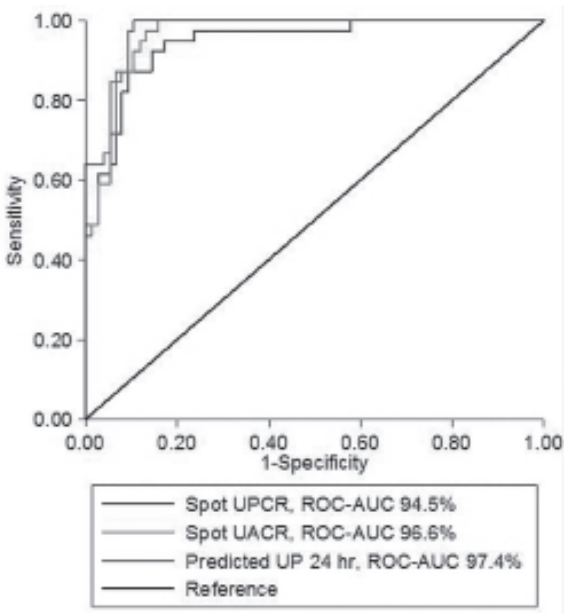

Fig. 2. Receiver operating characteristics curve of spot urine protein to creatinine ratio, spot urine albumin to creatinine ratio, and predicted 24-hour urine protein.

The multiple linear regression analysis for the predictive factors of the natural logarithm of UP-24 is presented in Table 2. The univariate analysis showed that the natural logarithm of UACR, natural logarithm of UPCR, body mass index, and underlying diabetes mellitus were significant factors. These factors and other factors with p-values less than 0.2, such as age and underlying chronic hypertension, were included in the initial multivariable linear regression model. The natural logarithm of UACR adjusted by age was a significant predictive factor for the natural logarithm of UP-24 in the final model. Using the linear equation from the final model of the multivariate linear regression analysis, the predicted UP-24 could be calculated from the following formula using spot UACR adjusted by age: Predicted UP-24 = Exp[3.179 + (0.019×age) + 0.476×Ln(UACR)].

The diagnostic performances of UACR, UPCR and predicted UP-24 in the detection of significant proteinuria are compared in Table 3 and Fig. 2. UP-24 was the reference standard at a cutoff value of 300 mg. The ROC-AUC of the predicted UP-24 was higher than that of UACR and UPCR (predicted UP-24, 97.4%; UACR, 96.6%; and UPCR, 94.5%). At the optimal cutoff value, the sensitivities of the predicted UP-24 and UACR (both 94.9%) were comparable, but the predicted UP-24 showed higher specificity than UACR (90.8% vs. 86.8%, respectively).

Table 2. Significant predictive factors for 24-hour urine protein identified by univariate and multivariate linear regression analysis.

Variables	Ln[UP-24 (mg)]		MD	95%CI	p value	Adj MD	95% CI	p value
	Mean	(SD)						
Age (years)	5.49	(1.11)	-0.02	-0.06, 0.01	0.132	0.02	0.01, 0.04	0.009
BMI (kg/m^2)	5.49	(1.11)	-0.04	-0.07, -0.01	0.016			
GA (weeks)	5.49	(1.11)	0.00	-0.04, 0.04	0.862			
DM					0.032			
No	5.63	(1.23)	Ref.					
Yes	5.15	(0.68)	-0.48	-0.92, 0.04				
CHT					0.077			
No	5.59	(1.16)	Ref.					
Yes	5.17	(0.89)	-0.42	-0.89, 0.05				
Time period of urine collection								
06.00-12.00 am	5.45	(1.11)	Ref.					
12.00-06.00 pm	5.52	(1.04)	0.06	-0.43, 0.55	0.800			
06.00-12.00 pm	5.43	(1.18)	-0.03	-0.59, 0.53	0.922			
Ln (UACR (mg/g))	5.49	(1.11)	0.46	0.42, 0.51	<0.001	0.48	0.44, 0.53	<0.001
Ln (UPCR)	5.49	(1.11)	0.75	0.66, 0.84	<0.001			

Adj, adjusted; BMI, body mass index; CHT, chronic hypertension; CI, confident interval; DM, diabetic mellitus; GA, gestational age; MD, mean difference; Ln, natural logarithm; SD, standard deviation; UACR, urine albumin to creatinine ratio; UP-24, 24-hour urine protein; UPCR, urine protein to creatinine ratio.

Table 3. Diagnostic performance of spot urine protein to creatinine ratio, spot urine albumin to creatinine ratio, and predicted 24-hour urine protein to indicate significant proteinuria.

Tests	ROC		p value	Cutoff value	Sn	Sp	PPV	NPV
	AUC (%)	95%CI			(%)	(%)	(%)	(%)
UPCR	94.5	90.4 - 98.6	Ref.	0.26	87.2	90.8	82.9	93.2
UACR (mg/g)	96.6	93.8 - 99.9	0.208	42	94.9	86.8	78.7	97.1
Predicted UP-24 (mg)	97.4	95.1 – 99.6	0.086	300	94.9	90.8	84.1	97.2

NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

Discussion

This study demonstrated that UACR and UPCR were significantly correlated with UP-24 (r = 0.884 vs. 0.834, respectively). These findings were comparable with those of previous studies showing that though UPCR was strongly correlated with UP-24 (r = 0.76-0.93)[9-12, 22, 23], UACR showed a stronger correlation with UP-24 (r = 0.94-0.95)[19, 20]. The correlation between UACR and UPCR was also highly significant (r = 0.90; p < 0.001), which was consistent with the results of a study by Cade et al[24].

A systematic review and meta-analysis[13, 18, 25] provided optimal cutoff values of UPCR ranging from 0.30 to 0.35 on average across all studies, with estimates of sensitivity and specificity ranging from 65% to 89% and 63% to 87%, respectively (pooled ROC-AUC, 69%). In contrast, the present study showed that UPCR had the highest ROC-AUC (94.5%) and a lower optimal threshold of 0.26 (87.2% sensitivity and 90.8% specificity). At an optimal cutoff of 42 mg/g, UACR exhibited good performance (ROC-AUC, 96.6%) for the diagnosis of significant proteinuria at a sensitivity of 94.9%, a specificity of 86.8%, a positive predictive value of 78.7%, and a negative predictive value of 97.1%. In this present study, UACR exhibited higher sensitivity than UPCR and may have indicated more significant cases of proteinuria.

Spot UACR adjusted by maternal age was significantly associated with the UP-24 results. UP-24 was better predicted by UACR adjusted for maternal age than by UACR (ROC-AUC, 97.4% vs. 96.6%, respectively). At an optimal threshold of 300 mg, the predicted UP-24 exhibited a high sensitivity of 94.9% and negative predictive value of 97.2%. These values were similar to those for UACR, but the predicted UP-24 showed a higher specificity of 90.8% and a positive predictive value of 84.1% compared with UACR. High sensitivity and negative predictive values supported the use of predicted UP-24 and UACR as effective alternative parameters in diagnosing significant proteinuria.

The strength of this study was the prospective enrollment of participants, which ensured that all urine samples were collected from inpatients, all tests were measured in the same laboratory, and all time collections were consistent. Both UACR and UPCR were measured in the same specimens. The adequacy of collection was assured by measuring the 24-hour urine creatinine. The authors chose to study random spot urine samples to represent routine practices. We preferred to study random spot urine samples instead of first void morning urine because the features of preeclampsia can present at any time, and waiting for the morning urine collection may have delayed the diagnosis. The spot urine samples for UACR and UPCR were obtained from women before starting the UP-24 collection; this approach aligned with clinical practices and decreased the potential for incomplete collection. The study population included a sufficient number of clinically relevant cases, including women with suspected, but not confirmed, preeclampsia and women with underlying pregnancy-associated diseases who were assessed over a standard collection time period. Moreover, this study presented the equation for adjusting the UACR based on the increasing correlation with the 24-hour urine protein collection and the diagnostic performance.

The limitations of the present study included the following. First, the laboratory was not available outside of office hours, and we were therefore unable to compare the timing of urine collection during all 24 hours. Second, UACR exhibited a greater correlation to UP-24 than UPCR; however, the difference was not statistically significant. A larger study population may have shown significant differences between these methods. Third, this study did not identify another excreted protein that may have differentiated the UACR and UPCR cases. Various types of urine proteins, such as Tamm-Horsfall glucoprotein and immunoglobulin, are noted during pregnancy. However, albuminuria exhibits increased glomerular endothelial permeability and thus may be an easily measured marker of endothelial dysfunction[20].

To summarize, both UACR and UPCR were significantly correlated with UP-24, but there was no significant difference between the diagnostic

performance of UACR and UPCR for significant proteinuria (95% CI; 93.8-99.9 and 90.4-98.6, respectively). Either of these markers may be a reasonable parameter for assessing proteinuria. Though UACR is a reliable test to detect proteinuria in pregnancy, future research may reveal more sensitive tests that determine albuminuria from urine globulins to diagnose preeclampsia. The data of this study did not support replacing UPCR with UACR during pregnancy; however, both methods could be used instead of UP-24 because they are simple, convenient, and accurate tests for measuring and estimating urine protein during pregnancy. The laboratory cost of UACR and UPCR in Rajavithi hospital were 150 and 100 Thai Baht, respectively. This research suggests that further studies are needed to determine the association between UACR and pregnancy outcome or the efficacy of the change in UACR in predicting preeclampsia in pregnant women with clinical symptoms.

Potential conflicts of interest

The authors declare no conflict of interest.

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