Original Article

The Use of Spot Urine Protein Creatinine Ratio in the Prediction of Severity and Adverse Pregnancy Outcome in Preeclampsia Women

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Objective: To determine the accuracy of spot urine protein to creatinine ratio (uPCR) in predicting preeclampsia with severe features and adverse maternal or neonatal outcomes.

Materials and Methods: The present research was a retrospective study. Thai pregnant women with diagnosis of preeclampsia that delivered at Thammasat University Hospital in Thailand between January 2014 and August 2018 were included in the present study. The uPCR was collected and determined in the subjects who had hypertension or the presence of positive urine protein dipstick. Demographic characters and maternal and fetal outcomes were collected and evaluated.

Results: Four hundred cases of preeclampsia were recruited in the present study. There were 185 and 215 cases of severe preeclampsia (SPE) and mild preeclampsia (MPE) or without SPE features, respectively. Both groups showed comparable demographic characters. Mean uPCR of SPE and MPE cases were 4.4 and 1.0, respectively, with statistical difference. The optimal threshold of uPCR for diagnosing proteinuria in the present study was 1.0. Sensitivity, specificity, and positive and negative likelihood ratio (LR+ and LR–) were 57.84%, 80.47%, 2.92, and 0.52, respectively. Pregnant women who had high uPCR had more cesarean delivery rate and adverse obstetrics outcomes than those with low uPCR.

Conclusion: Spot urine sample for uPCR was a useful test for proteinuria instead of waiting for 24 hours urine protein collection. The uPCR equal or greater than 1.0 could predict hazardous maternal and neonatal outcomes for immediate pregnancy management.

Keywords: Pregnancy, Preeclampsia, Urine protein to creatinine ratio

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Preeclampsia has been defined as hypertension (blood pressure more than 140/90 mmHg) after 20 weeks with proteinuria in previously normotensive pregnant women. Its incidence was reported around 4% to 5% of all pregnancies[1].

Twenty-four hours urine collection with higher than 300 mg protein has been defined as an important criteria for diagnosis of proteinuria, one of the factor contributing to preeclampsia[2]. This criterion was difficult to use in the clinical practice, and the 24 hours waiting caused delayed diagnosis.

Protein to creatinine ratio greater than 0.3 mg/dl has been suggested as a discriminator of women at risk of adverse outcomes[3]. However, this ratio does not provide any guideline for immediate case management. So far, there is no method of proteinuria assessment with strong association with the prediction of preeclampsia severity and adverse maternity outcome.

The present study investigated the possibility of using spot urine protein to creatinine ratio (uPCR) in preeclampsia prediction with adverse pregnancy outcomes in the authors' local population.

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Materials and Methods

The present retrospective study was approved by the Ethic Committee, Faculty of Medicine, Thammasat University, and MTU-EC-OB-1-029/61.

All singleton Thai pregnant women with diagnoses of preeclampsia that delivered at Thammasat University Hospital in Thailand between January 2014 and August 2018 were included. Diagnostic criteria for preeclampsia were blood pressure (systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more on two occasions at least four hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure, systolic blood pressure of 160 mmHg or more or diastolic blood pressure of 110 mmHg or more, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy), and proteinuria 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or uPCR of 0.3 mg/dL or more, or dipstick reading of 2+ (used only if other quantitative methods are not available)[2]. The uPCR test was available for widely service used in the authors' department since January 2014. Women were excluded from the study if they had pre-existing renal disease, co-existing urinary tract infection (defined by a positive mid-stream urine culture), twin pregnancy or patients who could not be followed throughout their pregnancy medical records.

The sample size in the present study was derived from the standard deviation (SD) between study and control group (SD 0.9) from Chan et al[4]. An alpha and beta value of 0.05 and 0.2 were used respectively. Four hundred cases were required by inclusion and diagnostic criteria[2].

The uPCR was collected and determined in the pregnant women who were hypertensive or yielded a positive urine protein dipstick. A sample for uPCR was collected in a random urine sample at any time of the day in the present study. Urine total protein was measured using a kinetics method based on reaction sequence, pyrogallol red combined with sodium molybdate to form a red complex. Urine creatinine was measured by using a kinetic colorimetric assay based on the Jaffé method. Both tests were performed with a Dimension clinical chemistry system (Siemens Healthcare Diagnostics GmbH, Cologne, Germany). The imprecision (coefficient of variation) of the urine protein assay was 7.4% at 20.4 mg/dL and 1.7% at 69.8 mg/dL, respectively.

For the primary outcome analysis, adverse maternal outcomes were represented by severe hypertension (blood pressure of 160/110 mmHg or greater), raised liver enzyme (alanine aminotransferase or aspartate aminotransferase 70 IU/L or greater), renal insufficiency (serum creatinine of more than 1.1 mg/dL), thrombocytopenia (platelet count of less than 100,000/μL), admission to intensive care unit (ICU), eclampsia, intracerebral hemorrhage, abruptio placentae, pulmonary edema, or maternal mortality. Adverse neonatal outcomes were represented by prematurity (delivery before 37 weeks' gestation), low birth weight (LBW) (less than 2,500 g), low Apgar score (less than 7) at 1 minute and 5 minutes of birth, admission to the neonatal intensive care unit (NICU), stillbirth, early neonatal death, or intrauterine growth restriction (IUGR). Data for maternal and neonatal outcomes were obtained from the hospital's clinical data analysis and reporting system and individual medical records. To minimize the effect of multiple pregnancies on the clinical outcome, only singleton pregnancies were included for outcome analysis. If more than one sample of uPCR were collected during the pregnancy, the first uPCR at the onset of proteinuria was used to determine the association with adverse outcomes. Data were analyzed by using Stata, version 14 (StataCorp LLC, College Station, Texas).

Continuous data were analyzed by using mean and unpaired t-test. Chi-square tests were used for categorical data. Level of statistical significance was set at p-valve less than 0.05. Sensitivity, specificity, and positive and negative predictive values of uPCR were calculated. The sensitivity and specificity of uPCR at different cut-offs were analyzed by receiver operating characteristics (ROC) curve. For the secondary outcome analysis, chi-square or Fisher's exact test was used to determine the difference in proteinuria level between cases with or without adverse pregnancy outcomes.

Results

The 400 cases of preeclampsia were divided into 185 and 215 cases with severe preeclampsia (SPE) and without SPE features or mild preeclampsia (MPE), respectively (Figure 1). Mean age and body mass index (BMI) of both groups were 31 years old and 29 kg/m², respectively, with no statistical difference (Table 1). Parity of both groups were compatible (nulliparity in SPE 50.2% and MPE 55.1%). Both groups showed no statistical significance in demographic data as presented in Table 1.

Members of both groups who had underlying diseases, namely overt diabetes mellitus, gestational diabetes mellitus (GDM), and thalassemia, which

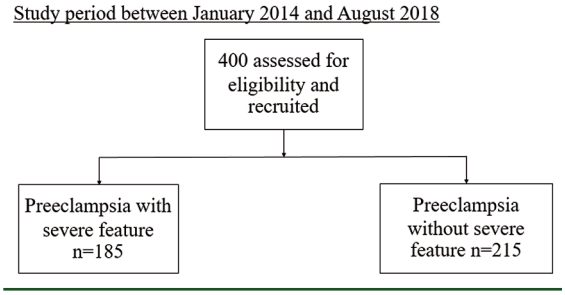

Figure 1. Participant flow diagram.

showed comparable severe feature of preeclampsia as shown on Table 1. Cases with underlying chronic hypertension (CHT) had more severe feature of preeclampsia than the cases without CHT (67.5% vs. 33.5%, p=0.004).

The preeclampsia cases with SPE had significant shorter onset of proteinuria than the other (36 versus 38 weeks) as shown at Table 1. Consequently, the gestational age of SPE cases was lesser than that of MPE by gestational age of delivery were 267±13 days and 253.9±22.5 days in SPE and MPE, respectively.

Mean uPCR of SPE and MPE cases were 4.4 and 1.0, respectively, with statistical difference. Cesarean delivery rate of SPE cases was significantly higher than the MPE cases (83.2% versus 60%). Mean birth weight of newborn in SPE mothers was 2,554.5±878.3 grams (p<0.001) compared to 3,071±601.4 grams in newborn from MPE mothers.

The receiver operating curve (ROC) was generated to determine the appropriate cut off point for uPCR. The area under ROC curve was chosen at level of 0.7507 (95% confidence interval [CI] 0.70286 to 0.79851) (Figure 2). The optimal threshold of uPCR for diagnosing proteinuria in the present study was 1.0. Sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR–) were 57.84%, 80.47%, 2.92, and 0.52, respectively. Comparison to the cut-off point from the literature (0.3), sensitivity, specificity, LR+, and LR– of the present study were

Table 1. General characteristics of study population (n=400)

Characteristic	Severe feature, Mean±SD		p-value
	Without (n=215)	With (n=185)	
Age (years)	31.2±6.6	31.5±6.2	0.71
BMI (kg/m^2)	29.5±6.2	29.2±6.0	0.72
Nulliparity, n (%)	108 (50.2)	102 (55.1)	0.33
Underlying disease, n (%)			
Overt DM	10 (58.82)	7 (41.18)	0.668
GDM	35 (58.33)	25 (41.67)	0.553
Thalassemia	4 (30.77)	9 (69.23)	0.091
CHT	13 (33.5)	27 (67.5)	0.004
Admission BP (mmHg)			
Systolic	148.5±10.4	163.8±15.5	<0.001
• Maximum	155.0±10.6	177.7±13.7	<0.001
Diastolic	95.4±8.4	104.1±11.3	<0.001
• Maximum	99.5±7.8	111.7±10.3	<0.001
GA (days)			
At onset of proteinuria	266.5±13.4	253.3±23.0	<0.001
At delivery	267±13	253.9±22.5	<0.001
uPCR	1.0±2.1	4.4±6.8	<0.001
CS, n (%)	129 (60.0)	154 (83.2)	<0.001
NBW	3,071.2±601.4	2,554.5±878.3	<0.001

SD=standard deviation; BMI=body mass index; DM=diabetes mellitus; GDM=gestational diabetes mellitus; CHT=chronic hypertension; BP=blood pressure; GA=gestational age; uPCR=urine protein to creatinine ratio; CS=cesarean section; NBW=newborn birth weight

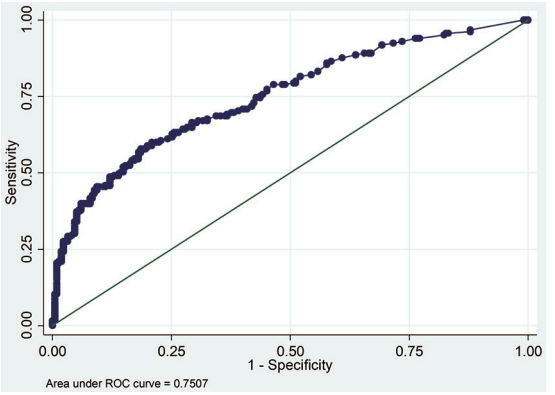

Figure 2. ROC curve of uPCR.

ROC: receiver operating curve, uPCR: urine protein to creatinine ratio

100%, 9.3%, 1.0, and 0.0, respectively, as shown in Table 2.

Correlation between spot urine protein-to-creatinine ratio and adverse pregnancy outcomes were represented in Table 3. Nearly a 100% (183 of 185) of cases with high uPCR (ratio of 1.0 or greater) suffered from severe hypertension (160/110 mmHg or more). Only half of the cases (98 of 215) with low uPCR (ratio of less than 1.0) developed severe hypertension. Liver and renal damaged were found in 10% and 1% in cases with high and low uPCR, respectively, as shown in Table 3. Thrombocytopenia, a catastrophic event that led to spontaneous hemorrhage especially in the brains, was found only in high uPCR group at 5% (9 of 185). Prevalence of eclampsia in the present

Table 2. Diagnostic performance of uPCR for predicting preeclampsia with severe feature

uPCR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR–
0.3	100	9.3	46.48	100	1.01	0
0.31	96.76	12.09	48.64	81.25	1.1	0.27
0.35	92.43	28.37	52.62	81.33	1.29	0.27
0.66	68.65	63.26	61.54	70.31	1.86	0.49
1.0	57.84	80.47	72	69.2	2.92	0.52
4.68	27.57	97.67	91.07	61.05	11.85	0.74
10.0	14.05	99.07	92.86	57.26	15.10	0.87

PPV=positive predictive value; NPV=negative predictive value; LR+=likelihood ratio positive; LR–=likelihood ratio negative; uPCR=urine protein to creatinine ratio

Table 3. Protein determined by uPCR in preeclampsia patient with and without adverse maternal complication (n=400)

Adverse maternal complication	uPCR, n (%)		p-value
	High (n=185)	Low (n=215)	
Abruptio placentae	1 (0.5)	1 (0.5)	0.92
Maternal death	0 (0.0)	0 (0.0)	NA
Severe hypertension	183 (98.9)	98 (45.6)	<0.001
Intracerebral hemorrhage	0 (0.0)	0 (0.0)	NA
PPH	7 (3.8)	5 (2.3)	0.39
Admission to ICU	3 (1.6)	0 (0.0)	0.061
Raised liver enzymes	17 (9.2)	1 (0.5)	<0.001
Renal insufficiency	19 (10.3)	2 (0.9)	<0.001
Thrombocytopenia	9 (4.9)	0 (0.0)	0.001
Eclampsia	4 (2.2)	0 (0.0)	0.03
Pulmonary edema	0 (0.0)	0 (0.0)	NA

uPCR=urine protein to creatinine ratio; PPH=postpartum hemorrhage; ICU=intensive care unit; NA=non accessibility
High: uPCR ≥1.0, Low: uPCR <1.0

Table 4. Protein determined by uPCR in preeclampsia patient with and without adverse neonatal complication (n=400)

Adverse neonatal complication	uPCR, n (%)		p-value
	High (n=185)	Low (n=215)	
Admission to NICU	53 (28.6)	27 (12.6)	<0.001
LBW	85 (45.9)	29 (13.5)	<0.001
Low APGAR score			
At 1 minute	16 (8.6)	5 (2.3)	0.005
At 5 minutes	9 (4.9)	4 (1.9)	0.091
Still birth	8 (4.3)	2 (0.9)	0.03
Prematurity	80 (43.2)	17 (7.9)	<0.001
IUGR	24 (14.6)	11 (5.1)	<0.001

uPCR=urine protein creatinine ratio; NICU=neonatal intensive care unit; LBW=low birth weight; IUGR=intrauterine growth restriction

High: uPCR ≥1.0, Low: uPCR <1.0

study was 1% (4/400), and was found only in the high uPCR group. Both high and low uPCR groups showed the non-significant occurrence of postpartum hemorrhage (PPH) and abruptio placentae. PPH and abruptio placentae were found in only 3% and 1% in the present study. There was no maternal death, pulmonary edema, or intracerebral hemorrhage case in the present study.

Participants with adverse neonatal outcomes and uPCR of preeclampsia were represented in Table 4. LBW (of less than 2,500 g) in the present study were 45.9% and 13.5% in high and low uPCR parturient, respectively, with statistical difference. The number of newborns with low APGAR scores at one minute of high uPCR mothers were significant higher than those of low uPCR mothers. Prematurity was the major problem in preeclampsia cases. It was found at 43.2% and 7.9% in high and low uPCR groups, respectively. Consequently, the number of admissions in neonatal intensive care needed in the high uPCR group was higher than that of the low uPCR group (28.6% versus 12.6%). Percent of stillbirth in the present study of the high and the low uPCR groups were 4.3% and 0.9%, respectively, with statistical difference. IUGR of high uPCR group was statistical higher than low uPCR group (14.6% versus 5.1%).

Discussion

SPE is one of the most hazardous condition of pregnancy. It consists of severe gestational hypertension and marked proteinuria. Definition of marked proteinuria came from the amount of protein measurement in a 24 hours urine protein collection. However, in many cases, the mothers delivered within 24 hours. Spot uPCR is a more practical and useful measurement.

Park et al reported in 2013 that uPCR greater than 4.68 could predict SPE with specificity and LR– at 85% and zero, as shown in Table 5[5]. Their work was conducted in 79 Korea pregnant women. This current study was conducted in 400 Thai pregnant women. The suggestion of uPCR cut-off point from the present study was 1.0, which gave specificity and LR– at 80.47% and 0.52. If the same cut-off point of Park's work was chosen, specificity and LR– would be at 97.67% and 0.74 for SPE prediction.

The application of uPCR for the prediction of SPE development in pregnant women with hypertension and proteinuria is easy and yields rapid result. The high specificity (true negative in all negative cases) and LR– test are desirable clinical applications. In women with low uPCR from the present study (cut-off point 1.0), the probability of negative SPE development was around 80%. In women with low uPCR, the unnecessary intensive care could be reduced.

A report from India in 2014 by Nischintha et al indicated that the uPCR cut-off point level of 0.3 gave sensitivity, specificity, and LR– at 100%, 12.5%, and 0, respectively[6]. They studied only 75 cases. The false negative (1-specificity) was around 87.5%. Compared to their work, the cut-off point from the present study (uPCR=1.0) was a better one as shown in Table 5.

A 2012 meta-analysis[7] by Morris et al suggested that uPCR greater than or equal to 0.3 could be used to predict the significant proteinuria (300 mg or more of protein in 24 hours urine), as seen in Table 5.

Table 5. Comparison of the present study to the previous literation

	Morris, et al.[7]	Park, et al.[5]	Nischintha, et al.[6]	Cheung, et al.[4]	The present study
Year	2012	2013	2014	2016	2018
Number of patients	2,978	140	75	120	400
Site	United Kingdom	Korean	India	Hong Kong	Thailand
Type	SM	R	P	R	R
Age (years)	NA	33.2	26.1	34	31
BMI (kg/m^2)	NA	NA	NA	22.8	29
GA at test (weeks)	NA	33.3	36.5	35	36
Nulliparity	NA	NA	NA	74.2	100
Type	Spot	Spot	Spot	24 hours	Spot
uPCR	0.3	4.68	0.66	33 mg/mmol	1.0
Sensitivity (%)	81	87.1	73.53	96	57.84
Specificity (%)	76	100	65.85	93	80.47
PPV (%)	NA	100	NA	98	72
NPV (%)	NA	58.7	NA	88	69.2
ROC	0.69	0.958	0.799	0.981	0.75
Maternal complication	H/L	H/L	H/L	H/L	H/L
SHT	NA	NA	NA	47/53	98.9/45.6
Eclampsia	NA	NA	1.3/0	NA	2.2/0
ICU	NA	NA	NA	16/84	1.6/0
LE	NA	NA	NA	6/94	9.2/0.5
CR	NA	NA	NA	6/94	10.3/0.9
LP	NA	NA	NA	2/98	4.9/0
Neonatal complication					
Admit NICU	NA	NA	37.9/44.4	54/46	28.6/2.6
LBW	NA	NA	43.9/22.2	60/40	45.9/13.5
Low APGAR					
• At 1 minute	NA	NA	21.2/0	21/79	8.6/2.3
• At 5 minutes	NA	NA	3/0	6/94	4.9/1.9
Still birth	NA	NA	NA	NA	4.3/0.9
Prematurity	NA	NA	NA	94/4	43.2/7.9
IUGR	NA	NA	NA	NA	14.6/5.1

R=retrospective study; P=prospective observational study; SM=systemic review and meta-analysis; NA=non accessibility; BMI=body mass index; GA=gestational age; uPCR=urine protein to creatinine ratio; Spot=spot urine protein to creatinine ratio; 24 hours=24 hours urine protein; PPV=positive predictive value; NPV=negative predictive value; ROC=receiver operating curve; H=high uPCR; L=low uPCR; SHT=severe hypertension; ICU=intensive care unit; LE=liver enzymes elevation; CR=creatinine rising; LP=low platelet; NICU=Neonatal intensive care unit; LBW=low birth weight; IUGR=intrauterine growth restriction

Compared to the present study, uPCR greater and equal than 1.0 could accurately predict SPE. Twenty-four hours urine protein was the gold standard for diagnosis significant proteinuria or SPE. Many studies tried to compare the uPCR to standard 24 hours urine protein because most cases of late preterm or term preeclampsia cases delivered less than or within 24 hours. At this point, a uPCR cut-off level of 0.3 should be used for screening the high risk to preeclampsia among the general population. The parturient who had uPCR equal or greater than 1.0 should highly be considered for adverse pregnancy outcome especially

with SPE. Cases having uPCR between 0.3 and 1.0 could be monitored less aggressively than those with higher uPCR.

The present study paid attention to uPCR ratio that predicted the maternal hazard outcomes. The high uPCR level cases (of 1.0 or more) had significant higher severe hypertension, raised liver enzymes, renal insufficiency, thrombocytopenia, and eclampsia. This finding had more clinical information for hazardous maternal outcomes prediction than 24 hours urine protein alone. In clinical practice, most 24 hours urine protein collection is nearly impossible because most mothers delivered less than 24 hours later.

Adverse neonatal outcome such as admission to NICU, LBW, low Apgar score at 1 minute, still birth, prematurity, and IUGR were the consequence of SPE. The authors assumed that high uPCR could predict hazardous maternal and neonatal outcomes for immediate pregnancy management.

The strength of the present study was the high number of enrolled and pregnant complication cases. The limitation of the present study was the lack of 24 hours urine protein reports due to the short delivery time.

Conclusion

Spot urine sample for uPCR was a useful test for proteinuria instead of waiting for 24 hours urine protein collection. The parturient who had uPCR equal or greater than 1.0 should be highly considered for adverse pregnancy outcome, especially with preeclampsia with severe feature (SPE). This value should be used for identifying the risk of severe outcomes in clinical practice. This test could reduce the unnecessary intensive care in low risk patients where the medical service resource is lacking or is insufficient.

What is already known on topic?

Preeclampsia was defined as hypertension after 20 weeks with proteinuria in previously normotensive pregnant women. Pregnant women who developed preeclampsia presenting severe features had high risk of maternal mortality and hazardous fetal outcomes. Twenty-four hours urine collection with higher than 300 mg protein has been defined as an important criterion for diagnosis of proteinuria. This criterion was a difficult one to use in the clinical practice and the 24 hours wait caused delayed diagnosis. Using spot urine sample for uPCR should be considered for condition prediction.

What this study adds?

Spot urine sample for uPCR was a useful test for proteinuria instead of waiting for 24 hours urine protein collection. The parturient who had uPCR equal or greater than 1.0 should highly be considered for adverse pregnancy outcome especially with preeclampsia with severe feature (SPE). The authors suggested that high uPCR could predict hazardous maternal and neonatal outcomes for immediate pregnancy management.

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Conflicts of interest

The authors declare no conflict of interest.

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