Diagnosis of proteinuria using a random urine protein-creatinine ratio and its correlation with adverse outcomes in pregnancy with preeclampsia characterized by renal damage

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Abstract

Based on a limited number of studies, a random urine protein-creatinine ratio (uPCR) value of ≥ 0.3 indicates abnormal proteinuria in preeclampsia with renal damage. However, current guidelines do not recommend a reasonable diagnostic threshold of uPCR for severe preeclampsia with renal damage. Furthermore, the correlation between the uPCR value and clinical adverse outcomes remains poorly understood. The aim of the present study was to evaluate the value of uPCR in the diagnosis of significant proteinuria and to assess its correlation with adverse pregnancy outcomes in preeclampsia characterized by renal damage. In all, 1837 women were enrolled in this retrospective cohort study. Eventually, 961 women were enrolled under the exclusion criteria. First, the authors found that uPCR and 24-hour proteinuria showed a significant association (r = 0.901). The optimal threshold of uPCR for diagnosing preeclampsia was 0.295, and for diagnosing severe preeclampsia the cut-off was 0.625. Meanwhile, the adjusted odds ratio per 1 unit increase in ln (uPCR) was 1.679 (95% confidence interval [CI]:1.142–2.469) for severe adverse perinatal outcomes; 1.456 (95% CI: 1.242–1.705) for small for gestational age; 1.380 (95% CI: 1.051–1.811) for severe small for gestational age; 1.672 (95% CI: 1.210–2.310) for very early preterm birth; 1.989 (95% CI 1.726–2.293) for severe hypertension; and 2.279 (95% CI 1.906–2.724) for preterm birth. This study indicated that there was a significant and positive correlation between uPCR and 24-hour urine protein. For neonatal and maternal adverse outcomes, uPCR is an independent predictor of prognosis.

KEYWORDS

perinatal outcome, preeclampsia, urine protein-creatinine ratio
Study design

Women's Hospital of Nanjing Medical University in China from March 2015-886). For the use of their data, all participants provided written informed consent.

2.1  |  Study design

The present study comprised a retrospective cohort study, which included all pregnant women undergoing regular check-ups in the Women's Hospital of Nanjing Medical University in China from March 2018 to April 2021 as the study population. The exclusion criteria comprised: (1) the presence of multiple pregnancies; (2) the participant suffered from renal disease, chronic hypertension, diabetes, or other complications before pregnancy; (3) within 1 month of sample collection, the participant used immunosuppressive drugs, glucocorticoids, or antibiotics; and (4) women carrying fetuses with major fetal anomalies. After 20 weeks of pregnancy, women diagnosed with hypertensive disorders of pregnancy were enrolled in our follow-up study until delivery. They were divided into three groups according to subsequent pregnancy outcomes: the gestational hypertension group, the PE group, and the SPE group. The demographic features of these pregnant women were recorded at the first visit, the clinical and laboratory data were collected at the time of subsequent antenatal visits, and the outcome of mothers and babies was collected for every pregnancy. uPCR measurements and other laboratory data were obtained close to the time of delivery and were used in the analysis. Urine samples for uPCR could be collected at any time during the day. Collection of 24-hour proteinuria samples was completed.

This study was reviewed and approved by the ethics review board of Women's Hospital of Nanjing Medical University (approval number, 2015-886). For the use of their data, all participants provided written informed consent.

2.2  |  Diagnostic criteria and variable definition

The diagnostic criteria for hypertensive disorders of pregnancy matched the criteria of the 2015 Chinese Society of Obstetrics and Gynecology guidelines, which were consistent with diagnostic criteria of the International Society for the Study of Hypertension in Pregnancy published in 2018. The gestational hypertension was defined as an average systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater, or both, which develops after 20 weeks of gestation, with no evidence of multisystem dysfunction (eg, clotting, liver, brain, and kidneys). PE is defined as gestational hypertension combined with proteinuria (dipstick reading of at least 1+ or 300 mg of protein in a 24-h urine collection) or with one or more injured organs. SPE is defined as PE combined with severe hypertension (defined as systolic blood pressure of 160 mm Hg or diastolic blood pressure of 110 mm Hg), or combined with at least one of the following other symptoms: Fetal growth restriction, cerebral or visual symptoms, pulmonary edema, cardiac insufficiency, impaired liver function (liver transaminases levels twice normal), renal insufficiency (urine protein excretion of \( \geq 2 \) g/24 h or creatinine > 1.1 mg/dL), hypoalbuminemia, and thrombocytopenia (platelets < 100 k/ml). We prespecified six primary outcomes on the basis of importance: (1) Severe adverse perinatal outcomes, defined as one or more of: pulmonary edema, placental abruption, eclampsia, disseminated intravascular coagulation, HELLP (hemolysis, elevated liver enzymes, low platelets), cardiac insufficiency, neonatal asphyxia (Apgar score < 7 at 5 min) or fetal death; (2) birth prior to 34 weeks of gestation was defined as very early preterm birth; (3) small for gestational age was defined as a birth weight of < 10th percentile for gestational age; (4) severe small for gestational age was
defined as a birth weight of < 3rd percentile for gestational age; (5) cerebral symptoms; and (6) renal insufficiency or impaired liver function.

Secondary outcomes, including obstetric and perinatal complications, were as follows: Preterm birth, specified as birth prior to 37 weeks of gestation; severe hypertension; oligohydramnios (the volume of amniotic fluid is abnormally low (< 300 ml) in late pregnancy); postpartum hemorrhage (more than 500 ml of vaginal bleeding in 24 h following fetal delivery); hypoalbuminemia (Plasma albumin < 30 g/L); thrombocytopenia (platelets < 100 k/ml); chorioamnionitis; and fetal distress.

### 2.3 Data analysis

SPSS 24 statistical software was used to analyze the data (IBM Corp., Armonk, NY, USA). Continuous statistics were expressed as the mean±standard deviation. To analyze the data among more than two groups, we used one-way analysis of variance. Categorical statistics, which are shown as frequencies with proportions, were analyzed using Fisher’s exact test or the chi-squared test as appropriate. Non-normally distributed quantitative data are presented as the median and quartile range and were analyzed using the Kruskal–Wallis H test. Pearson’s correlation coefficient was used to evaluate the relationship between uPCR and 24-hour proteinuria after logarithmic transformation to account for the fact that the data distribution of the two parameters was not nominal. Receiver operating characteristic (ROC) curves were used to assess how the uPCR test performed in diagnosis. As a cut-off value for PE diagnosis, the optimal uPCR value was determined using the maximum sensitivity, specificity, negative predictive value, and positive predictive value. The unadjusted and adjusted prognostic associations of each primary and secondary outcome with the uPCR value were assessed using univariate and multivariate logistic regression models. The logistic models assessed uPCR’s prognostic value using an (adjusted) odds ratio, representing the (adjusted) relative odds of the outcome for two women that differ in their log-uPCR values by 1 unit. A two tailed p-value of < .05 was considered statistically significant.

### 3 RESULTS

For the final analysis, 961 pregnant women with hypertensive disorders of pregnancy who met the inclusion criteria were recruited. Among them, 297 were diagnosed with gestational hypertension, 261 with PE, and 403 with SPE (Figure 1). The data in Table 1 shows that the three groups had similar body mass index values at delivery. The SPE group was older and had a lower pre-pregnancy body mass index. Although the PE group showed a higher percentage of in vitro fertilization than the other two groups (P = .047), there was no significant difference between any two groups. The percentage of nulliparity and smoking did not differ significantly among the three groups. The SPE group showed higher blood pressure than the other two groups. For the major clinical indicators of renal function, including, uPCR, Creatinine, and urea nitrogen, the SPE group showed significantly higher scores than the other two groups (P < .05).

The analysis of the relationship between uPCR and 24-hour proteinuria was limited to data from participants whose 24-hour proteinuria collections were completed (A total of 594 specimens were collected). The uPCR value and the 24-hour proteinuria scores correlated significantly (r = 0.901, P = .000) (Figure 2). The optimal threshold of uPCR to diagnose PE was 0.295 (sensitivity = 79.1%, specificity = 90.7%, positive predictive value = 94.9%, and negative predictive value = 66.5%) and to diagnose SPE it was 0.625 (sensitivity = 79.3%, specificity = 91.5%, positive predictive value = 74.9% and negative predictive value = 79.7%) (Table 2). The areas under ROC curve were 0.890 (95% CI, 0.870–0.910) and 0.819 (95% CI, 0.791–0.847) for PE and SPE, respectively (Figure 3).

The analysis of the relationship between uPCR and adverse maternal and infant outcomes was limited to data from participants with PE. Among participants with PE, 27 experienced a severe adverse perinatal outcome (2.81%) and four had more than one adverse event (Table 3). Table 4 shows the statistically significant unadjusted and adjusted prognostic values of ln (uPCR) for primary adverse outcomes. The adjusted odds ratio (aOR) per 1 unit increase in ln (uPCR) was 1.679 (95% CI: 1.142–2.469) for severe adverse perinatal outcomes; 1.456 (95% CI: 1.242–1.705) for small for gestational age; 1.380 (95% CI: 1.051–1.811) for severe small for gestational age; 1.672 (95% CI: 1.210–2.310) for very early preterm birth. The results for the secondary outcomes are shown in Table 5. uPCR was identified as an independent prognostic factor for severe hypertension (aOR 1.989, 95% CI 1.726–2.293) and preterm birth (aOR 2.279, 95% CI 1.906–2.724).

### 4 DISCUSSION

PE occurs in about 5–7% of all pregnancies, and is often accompanied by renal complications. Although symptoms decrease after delivery, permanent kidney damage has been reported, and women with PE commonly develop acute kidney injury, which is associated with high rates of maternal and perinatal mortality. Thus, it is important to recognize and treat PE and related renal syndromes early. Currently, as a primary symptom of PE characterized by renal damage, proteinuria has become a sufficient, but nonessential, marker to diagnose PE. In 2013, the American college of obstetricians and gynecologists deleted proteinuria severity from the list of criteria used to diagnose PE. However, according to the International Society for the Study of Hypertension in Pregnancy, more severe neonatal outcomes are related to proteinuria. Meanwhile, Proteinuria is still one of the diagnostic criteria for SPE in China.

Consistent with previous studies, our findings indicated that uPCR and 24-hour proteinuria correlated strongly (r = 0.901). This suggests that it is theoretically feasible to use uPCR to replace 24-hour proteinuria in clinical practice. Using uPCR produced an average ratio of proteinuria, which allowed the accurate assessment of the 24-hour proteinuria value. Meanwhile, ROC curve analysis identified 0.295 as the best uPCR threshold to detect urine protein
## TABLE 1  Clinical characteristics of three groups

| Characteristic                | GH (n = 297) | PE (n = 261) | SPE (n = 403) | p     |
|------------------------------|--------------|--------------|---------------|-------|
| Age (year) (M ± SD)          | 30.28 ± 4.07 | 30.18 ± 4.30 | 30.95 ± 4.51  | .039  |
| BMI before pregnancy (M ± SD)| 23.69 ± 3.79 | 23.72 ± 3.68 | 22.94 ± 3.61  | .027  |
| BMI at delivery (M ± SD)     | 29.22 ± 4.06 | 29.64 ± 3.67 | 29.11 ± 3.91  | .207  |
| Nullipara (n/%)              | 236 (79.4)   | 220 (84.2)   | 285 (71)      | .190  |
| IVF (n/%)                    | 33 (11.1)    | 48 (18.4)    | 51 (12.7)     | .047a |
| Smoking history              | 8 (2.6)      | 7 (2.6)      | 15 (3.7)      | .573  |
| Use of anti-hypertensive drugs (n/%) | 68 (22.9) | 95 (36.4) | 332 (82.4) | .000 |
| Peak SBP (mm Hg) (M ± SD)    | 142.57 ± 11.62 | 145.72 ± 9.33 | 161.30 ± 12.58 | .000 |
| Peak DBP (mm Hg) (M ± SD)    | 93.97 ± 7.97  | 94.29 ± 6.84 | 102.89 ± 9.60 | .000 |
| uPCR median (interquartile range) | 0.17 (0.13–0.23) | 0.45 (0.28–0.85) | 1.44 (0.42–2.69) | .000 |
| Creatinine (mg/dl) (M ± SD)  | 3.76 ± 1.07   | 4.05 ± 1.25  | 4.86 ± 1.73   | .000 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GH, gestational hypertension; IVF, in vitro fertilization; M ± SD, mean ± the standard deviation; PE, preeclampsia; SBP, systolic blood pressure.; SPE, severer preeclampsia.

*There was no significant difference between any two groups.

## TABLE 2  Sensitivity, specificity, PPV, and NPV for different cut-offs

| Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---------|-----------------|-----------------|---------|---------|
| PE      | 0.295           | 79.1            | 90.7    | 94.9    | 66.5    |
| SPE     | 0.625           | 68.8            | 84.2    | 74.9    | 79.7    |

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

*Data from participants whose 24-hour proteinuria collections were completed.

## TABLE 3  Number of severe adverse perinatal outcomes

| Maternal                     | Numbers | neonatal                                | Numbers |
|------------------------------|---------|-----------------------------------------|---------|
| eclampsia                    | 0       | fetal death                             | 3       |
| placental abruption          | 2       |                                          | 6       |
| HELLP                        | 1       | neonatal asphyxia (Apgar score < 7 at 5 min) | 9       |
| DIC                          | 1       |                                          |         |
| Cardiac insufficiency        | 8       |                                          |         |
| pulmonary edema              | 2       |                                          |         |

Abbreviations: DIC, disseminated intravascular coagulation.; HELLP, hemolysis, elevated liver enzymes, low platelets.

*Only women with preeclampsia were included.

## TABLE 4  Unadjusted and adjusted prognostic value of ln (uPCR) for primary adverse outcomes

| Primary outcomes                          | Unadjusted OR (95% CI) | p     | Adjusted OR (95% CI) | p     |
|-------------------------------------------|------------------------|-------|----------------------|-------|
| Severe adverse perinatal outcome          | 2.185 (1.568–3.045)    | .000  | 1.679 (1.142–2.469)  | .008  |
| Small for gestational age                 | 1.871 (1.623–2.157)    | .000  | 1.456 (1.242–1.705)  | .000  |
| Severe small for gestational age          | 1.478 (1.150–1.898)    | .002  | 1.380 (1.051–1.811)  | .020  |
| Renal or liver insufficiency              | 1.505 (1.153–1.964)    | .003  | 1.264 (0.944–1.693)  | .115  |
| Very early preterm birth                  | 3.137 (2.450–4.015)    | .000  | 1.672 (1.210–2.310)  | .002  |
| Cerebral symptoms                         | 1.295 (0.999–1.679)    | .051  | 1.218 (0.916–1.620)  | .175  |

*Only women with preeclampsia were included; Data are adjusted for maternal age, BMI before pregnancy, parity, mode of conception and gestational age at diagnosis of preeclampsia in multiple logistic regressions.
excretion ≥ 0.3 g/24 h, with 79.1% sensitivity and 90.7% specificity. This threshold is consistent with the recommended guidelines. Another study also suggested that uPCR could replace 24-hour proteinuria to diagnose proteinuria in PE. In addition, it was proposed that uPCR could estimate the magnitude of proteinuria, particularly in SPE. On this basis, we revealed that to diagnose SPE, the optimal uPCR threshold was 0.625, with 90.6% sensitivity and 99.6% specificity. According to previous research, a uPCR value above 500 mg/g is considered to indicate severely increased albuminuria, which was similar to our results. In our study, better sensitivity and specificity in the diagnosis of SPE was also observed. This might indicate that, similar to a previous study, uPCR detects massive proteinuria more sensitively and more specifically. To the best of our knowledge, this was the first report to demonstrate the diagnostic accuracy of uPCR for SPE characterized by renal damage.

There is considerable debate as to whether preeclampsia with varying degrees of proteinuria results in different outcomes, as the impact of urinary protein on clinical decision making decreases.
Some studies noted that uPCR might cause maternal and neonatal adverse outcomes in PE with renal damage, such as small-for-gestational age, preterm delivery, liver disease, renal insufficiency, and severe hypertension. However, a multicenter study demonstrated that adverse perinatal outcome could not be predicted using uPCR or 24-hour proteinuria output. Thus, we further determined whether uPCR is a prognostic indicator for adverse neonatal and maternal outcomes.

The primary analyses included "composite outcomes," which were designed to increase the power to detect uPCR's prognostic ability because of the small number of severe adverse perinatal outcomes. The primary results suggested that a 1 unit increase in the log-transformed uPCR was associated with an increase in the risk of severe adverse perinatal outcomes by 67.9%. This showed that uPCR was associated with severe adverse perinatal outcomes in PE characterized by renal damage, and when preeclampsia was complicated with renal damage, HELLP, placental abruption, and eclampsia are more likely to occur, together with high perinatal mortality. In addition, a 1 unit increase in the log-transformed uPCR value was associated with an increased risk of severe small for gestational age of 38% and an increased risk of small for gestational age of 45.6%. Another study also indicated that a proteinuria threshold above 300 mg/24 h is associated with an increased risk of small for gestational age < 5th centile compared with women with hypertension but without proteinuria. The loss of a large amount of protein in the mother and the insufficient supply of protein and other nutrients might lead to fetal intrauterine growth restriction and low birth weight. In addition, uPCR was associated with very early preterm birth, which was similar to the results of a previous study. Proteinuria test results have less influence on the decision regarding the timing of delivery management; therefore, a large uPCR might increase maternal complications and lead to earlier delivery.

According to the secondary analyses, there was an important correlation between uPCR and severe hypertension. Overall, compared with women with hypertension or mild preeclampsia, women with severe gestational hypertension had more adverse perinatal outcomes. Therefore, uPCR can be used to evaluate the severity of PE in patients with renal damage. The occurrence of hypoproteinemia indicates further aggravation of the disease, which could affect the function of each organ. In our study, we found that uPCR was associated with hypoalbuminemia; therefore, we suggested that uPCR could reflect the deterioration of the disease. In conclusions, for neonatal and maternal adverse outcomes, we suggest that uPCR is an independent prognostic factor.

5 CONCLUSIONS

For PE with renal damage, 24-hour proteinuria correlated positively and significantly with uPCR. For maternal and neonatal adverse outcomes, uPCR was identified as an independent prognostic factor. Therefore, in patients with preeclampsia, uPCR-based diagnosis of
significant proteinuria is simpler, faster, and more useful compared with using the 24-hour proteinuria.

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CONFLICT OF INTEREST
The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS
Zhonghua Shi designed and conceived the study, acquired the funding, and edited the manuscript; Jiangbo Xiao and Weimin Fan analyzed the data and wrote the manuscript; Qingyi Zhu contributed to the data collection.

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