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ORIGINAL ARTICLE

Correlation of Urine Protein/Creatinine Ratio in Late Pregnancy with Pregnancy Outcome in Patients with Preeclampsia Combined with Hyponatremia

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SUMMARY

Background: **This study aimed to analyze the correlation of urine protein/creatinine ratio (UPCR) in late pregnancy with pregnancy outcomes in patients with preeclampsia (PE) combined with hyponatremia.**
Methods: **The data of 288 PE patients were collected and compiled for retrospective analysis. The patients were divided into two groups: observation group (52 cases, complicated with hyponatremia) and control group (236 cases, not complicated with hyponatremia). The general conditions, clinical data, and the adverse maternal and infant outcomes were statistically analyzed in both groups. Risk factors were analyzed using logistic regression, and the predictive efficacy was assessed using the ROC curves.**
Results: **Comparing the general data of the two groups, the differences were not statistically significant (all $p > 0.05$). Multifactorial analysis showed that uric acid (OR = 0.001, $p = 0.010$) and 24-hour urinary protein (OR = 2.654, $p = 0.001$) were the independent risk factors for hyponatremia in PE. In the observation group, placental abruption (9.6%, $p = 0.015$), hepatic and renal impairment (38.6%, $p < 0.001$), pleural effusion (30.7%, $p = 0.001$), fetal growth restriction (50.0%, $p = 0.001$), fundus lesions (7.6%, $p = 0.012$), HELLP syndrome (7.7%, $p = 0.017$), mild neonatal asphyxia (17.3%, $p = 0.025$), severe asphyxia (3.8%, $p = 0.046$), metabolic acidosis (9.6%, $p = 0.001$), intrauterine infection (5.7%, $p = 0.004$), and neonatal hospitalization exceeding 20 days (30.7%, $p < 0.001$) occurred in a higher percentage than in the control group. There was no significant difference in postpartum hemorrhage, eclampsia, respiratory distress syndrome, abortion, or neonatal death (all $p > 0.05$).**
Conclusions: **The UPCR in late pregnancy is an independent risk factor for hyponatremia in PE. Patients with PE combined with hyponatremia are at high risk of adverse maternal and infant outcomes.**
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KEYWORDS

preeclampsia, hyponatremia, pregnancy, urine protein/creatinine ratio

INTRODUCTION

Preeclampsia (PE) is a common pregnancy-specific syndrome characterized by generalized edema, hypertension, and proteinuria during pregnancy with progressive development, and its incidence rate is 3 - 5%

in a global perspective [1]. Patients with PE are usually accompanied by a variety of organ dysfunctions, including cardiac, renal, and hepatic, and the fetus exhibits placental hypoplasia, hypoxia, growth restriction complications such as placental abruption and preterm labor, as well as long-term complications such as cerebral palsy and chronic pulmonary hypertension [2,3]. PE is often life-threatening if it is not diagnosed and treated in a timely manner [4].

As one of the main damaged target organs in PE, kidney function, once impaired, often seriously affects maternal and fetal health and even causes chronic renal failure [5]. Hyponatremia refers to serum sodium concentration less than 135 mmol/L and is the most common electrolyte disorder in clinical practice. Hyponatremia can be secondary to a variety of diseases, and the clinical manifestations lack specificity, which can be easily masked by the primary disease [6]. Hyponatremia is common in patients with PE, which may be due to abnormal renal aldosterone response, changes in body fluid distribution, and the role of angiotensin II, resulting in increased sodium excretion and decreased blood volume, further exacerbating the complexity of the disease [7,8]. To promote maternal and fetal health, early detection, intervention, and treatment of renal dysfunction are essential [9]. At present, the main means of clinical evaluation of PE is the detection of maternal urinary protein, blood pressure, and involvement of diseased organs, and the level of urinary protein has also become an important indicator for the classification of mild and severe PE [10].

The aim of this study was to explore the relationship between the urine protein/creatinine ratio (UPCR) in late pregnancy and pregnancy outcome in patients with PE combined with hyponatremia. We hypothesized that the UPCR might serve as a biomarker for predicting the severity of PE complicated by hyponatremia and adverse pregnancy outcomes. By testing this hypothesis, we hope to inform clinical practice to identify high-risk pregnant women earlier, so that timely interventions can be implemented to improve maternal and infant health outcomes.

MATERIALS AND METHODS

General information

The data of 288 PE patients who were hospitalized and delivered in Ganzhou Women and Children's Health Care Hospital from March 2021 to March 2024 were collected and compiled for retrospective analysis. The patients were divided into two groups: observation group (52 cases, complicated with hyponatremia) and control group (236 cases, not complicated with hyponatremia). The age of the observation group ranged from 22 to 44 years, with an average age of 33.48 ± 3.85 years, and the gestation period was 25 - 31 weeks, with an average gestation period of 28.77 ± 2.03 weeks. In the control group, the age was 23 - 42 years, the average age was (33.34 ± 3.89) years, the gestational weeks were 26 - 31 weeks, and the average gestational weeks were (28.81 ± 1.97) weeks. The general data of the two groups were comparable, with no statistically significant differences ($p > 0.05$). PE diagnosis was in accordance with the diagnostic criteria for PE [11].

Inclusion criteria: 1) compliance with the diagnosis of PE; 2) complete case data; and 3) age range 18 - 45 years. Exclusion criteria: 1) pre-pregnancy or pregnancy found to be combined with cardiovascular disease, autoimmune system and endocrine system diseases, and other serious medical diseases; 2) pregnancy combined with chronic cryptogenic nephritis; 3) pregnancy combined with history of psychiatric disorders; 4) pregnancy combined with tumors; and 5) incomplete data. The study was conducted with the informed consent of the patients and approved for execution after review by the Ethics Committee of Ganzhou Women and Children's Health Care Hospital.

Measurement of the UPCR

The first morning urine, 24-hour urine, and random urine were collected within 2 days. The first morning urine was collected on the first day and the morning UPCR was detected, and the detecting time T was recorded. All urine was left in a container until the second day of T, and 24-hour urine protein quantification was detected. On the morning of the second day, a random urine sample was taken to detect the random UPCR. Urinary protein was determined by modified bis-urea colorimetry, and urinary creatinine was determined by Jaue kinetic method, Hitachi 7170 automatic biochemical analyzer, and reagents from BIOSINO (Beijing, China).

Statistical analysis

IBM SPSS Statistics 26.0 statistical software was used. The quantitative data were normally distributed and expressed as mean ± standard deviation. Data comparison was done using independent sample *t*-test or rank sum test. The qualitative data were tested by chi-squared test. The correlation between UPCR value and urinary protein quantification was tested by Pearson's correlation analysis, and the correlation between biochemical indexes, the occurrence of renal impairment, and poor prognosis was tested by Spearman's correlation method. The receiver operating characteristic (ROC) was used for the assessment of poor prognosis by UPCR, and Youden index = specificity + sensitivity-1, and the maximum value of Youden index was taken as the optimal diagnostic threshold for determining poor prognosis based on UPCR. $p < 0.05$ indicated that the difference was statistically significant.

Table 1. Comparison of the general conditions between the two groups of preeclampsia patients.

Groups	n	Age ≥ 35	Number of pregnancy ≥ 3	Cesarean section history	Assisted reproduction	Twin pregnancy	Primiparity	Gestational diabetes mellitus	Adverse pregnancy history	Chronic hypertension
Control group	236	70	98	60	33	21	85	68	57	32
Observation group	52	9	20	5	5	5	9	10	7	1
χ^2 value		0.45	2.39	2.58	0	0.36	2.05	0.04	0.49	2.63
p-value		0.502	0.122	0.108	0.964	0.547	0.121	0.83	0.482	0.105

*** - compared with control group, $p < 0.05$.**

Table 2. Analysis of clinical data of the two groups.

Groups	n	Age	Admission systolic blood pressure	Admission diastolic blood pressure	Mean arterial blood pressure	Pre-pregnancy body mass index	Hospital-ization time	Termination of pregnancy
		Years	mmHg	mmHg	mmHg	kg/m^2	Days	Weeks
Control group	236	33.15 ± 6.12	158.23 ± 16.42	100.00 ± 13.02	92.63 ± 12.34	22.86 ± 3.45	5.89 ± 3.21	36.25 ± 3.25
Observation group	52	32.16 ± 5.69	163.23 ± 20.12	108.40 ± 11.65	89.23 ± 9.12	21.85 ± 2.99	7.82 ± 3.64	34.46 ± 3.80
t value		0.28	-1.56	-1.98	0.76	1.58	-2.52	3.39
p-value		0.792	0.185	0.008	0.502	0.121	0.008	0.002
Groups		Prenatal glucose	Blood urea	Creatinine	24 Urinary protein	Albumin	Uric acid	Hemoglobin
		mmol/L	mmol/L		g	g/L	mmol/L	g/L
Control group	236	5.39 ± 1.25	7.0 ± 1.26	95.31 ± 30.19	1.94 ± 2.61	35.84 ± 10.77	398.65 ± 103.79	234.81 ± 70.79
Observation group	52	5.72 ± 1.26	7.96 ± 4.36	99.80 ± 32.23	5.26 ± 3.43	42.83 ± 8.31	452.65 ± 82.63	199.84 ± 86.97
t (Z) value		-1.23	(-3.62)	2.58	(-5.90)	(-3.78)	(-2.98)	2.36
p-value		0.026	0.001	0.013	0.001	0.001	0.008	0.015

Table 3. Logistic regression analysis of related factors of preeclampsia patients with hyponatremia.

Indexes	Regression coefficient	Standard deviation	Wald	p-value	OR value	95% CI
24-hour urinary protein	0.226	0.067	3.393	0.001	2.654	1.123 - 1.698
Uric acid	0.008	0.003	3.13	0.01	0.001	1.009 - 1.188
Constant	-4.005	0.502	52.36	0.001	0.01	

RESULTS

General conditions

When comparing the two groups, the difference was not statistically significant ($p > 0.05$, Table 1).

Clinical data

When comparing the continuous variables between the two groups, the observation group had higher values than the control group in terms of admission diastolic blood pressure, days of hospitalization, weeks of preg-

Table 4. Comparison of the incidence of pregnancy complications between the two groups of preeclampsia patients [case (%)].

Groups	n	Eclampsia	Placental abruption	FGR	Hepatic and renal impairment	Pleural effusion	Fundus lesions	Postpartum hemorrhage	HELLP syndrome
Control group	236	3 (1.2)	3 (1.2)	52 (22.1)	25 (10.6)	18 (7.6)	0 (0.0)	12 (5.1)	3 (1.2)
Observation group	52	0 (0.0)	5 (9.6)	26 (50.0)	20 (38.6)	16 (30.7)	4 (7.6)	5 (9.6)	4 (7.7)
χ^2 value				11.39	13.59	10.98		1.08	
p-value		1.000a	0.015	0.001	< 0.001	0.001	0.012	0.393	0.0017

Eclampsia, placental abruption, fundus lesions, HELLP, etc. for at least one theoretical frequency < 1. Data analysis was done with Fisher's exact method for analysis; HELLP syndrome - hemolysis, elevated liver enzymes, low platelets.

Table 5. Comparison of the incidence of neonatal adverse outcomes between the two groups of preeclampsia patients [case (%)].

Groups	n	Mild asphyxia	Severe asphyxia	Fetal or neonatal death	Metabolic acidosis	Respiratory distress syndrome	Neonatal hospitalization over 20 days	Intrauterine infection
Control group	236	12 (5.1)	1 (0.4)	9 (3.8)	3 (1.2)	21 (8.9)	25 (10.5)	2 (0.8)
Observation group	52	9 (17.3)	2 (3.8)	3 (5.7)	5 (9.6)	11 (21.1)	16 (30.7)	3 (5.7)
χ^2 value		4.69		0	8.69	3.01	15.26	7.98
p-value		0.025	0.046	0.899	0.001	0.078	< 0.001	0.001

The theoretical frequency of severe asphyxia is less than 1, which needs to be analyzed by Fisher exact method. The remaining indicators have a theoretical frequency of 1 - 5, and χ^2 test is used for analysis.

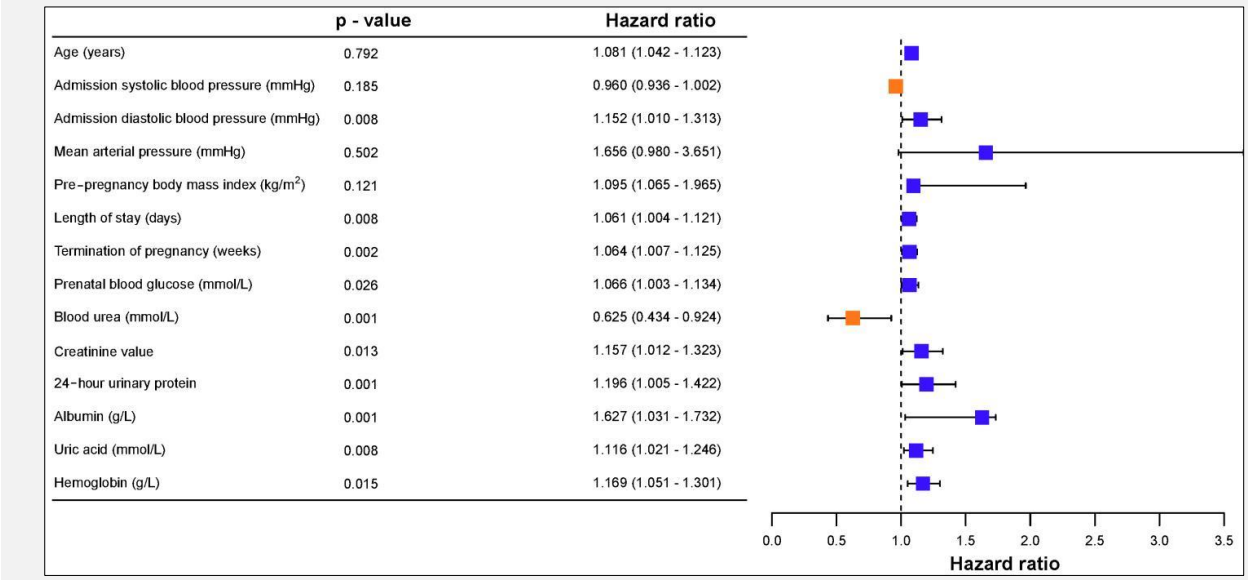

Figure 1. Forest plot analysis of the clinical data of the two groups.

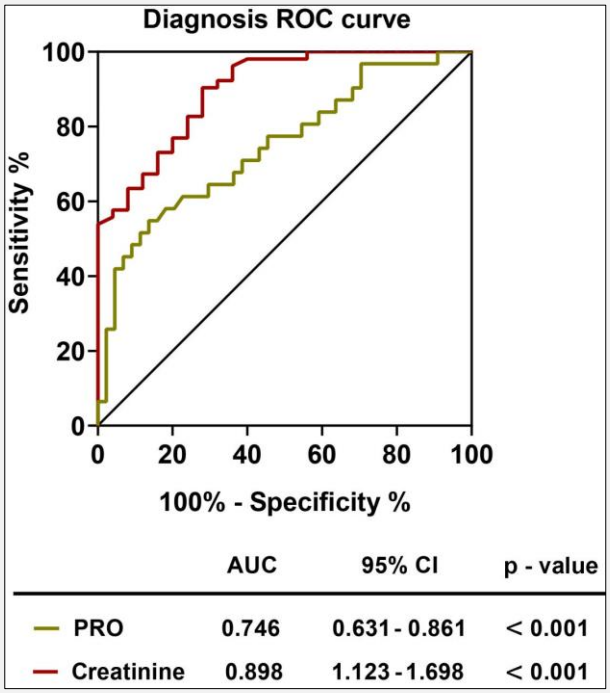

Figure 2. ROC curve of urinary protein/creatinine ratio to predict PE combined with hyponatremia.

nancy termination, prenatal blood glucose, blood urea, creatinine value, 24-hour urinary protein, albumin, and uric acid, while it presented lower values in terms of hemoglobin (all $p < 0.05$, Table 2 and Figure 1).

Multifactorial logistic regression analysis

Indicators with statistically significant differences analyzed by *t*-test and χ^2-test were included as independent variables, including age, admission systolic blood pressure, admission diastolic blood pressure, mean arterial blood pressure, pre-pregnancy body mass index, days of hospitalization, weeks of termination of pregnancy, prenatal glucose (mmol/L), blood urea, creatinine value, 24-hour urinary protein, albumin, uric acid, and hemoglobin. Multifactorial logistic regression analyses were performed with the dependent variable of hyponatremia (YES/NO). The results showed that uric acid ($p = 0.010$, OR = 0.001, 95% CI = 1.009 - 1.188) and 24-hour urinary protein ($p < 0.001$, OR = 45.63, 95% CI = 1.123 - 1.698) were the risk factors for hyponatremia in patients with PE, and the higher the relevant values, the higher the risk of hyponatremia (Table 3).

ROC analysis results

ROC analysis confirmed that the late pregnancy UPCR was useful to predict late pregnancy PE combined with hyponatremia, and the ROC curve of UPCR to predict late pregnancy PE combined with hyponatremia is shown in Figure 2.

Maternal and fetal outcomes

The incidence of placental abruption, hepatic and renal impairment, pleural effusion, fundus lesions, FGR, and HELLP syndrome in the observation group was higher than those in the control group (all $p < 0.05$), as shown in Table 4. The incidence of neonatal asphyxia, metabolic acidosis, intrauterine infection, and neonatal hospitalization days over 20 days in the observation group was higher than those in the control group (all $p < 0.05$, Table 5).

DISCUSSION

Hypertensive disorders of pregnancy are complications specific to pregnancy [12]. PE is one of the most important causes of increased maternal and infant morbidity and mortality during pregnancy [12,13]. Hyponatremia is a very rare complication of PE with relatively few reported cases. However, there are currently very limited domestic and international treatments for PE combined with hyponatremia. This study focused on the occurrence and development process of PE

combined with hyponatremia and actively searched for the factors associated with it.

PE combined with hyponatremia, in most studies, affects pregnant women early in the pregnancy and has a poor prognosis [14,15]. In the present study, patients with PE combined with hyponatremia had a significantly higher incidence of severe maternal and fetal adverse events. Na^+ and Cl^- constitute the major components of plasma crystal osmolality. When the plasma Na^+ concentration decreases, the plasma crystal osmotic pressure decreases, the cells swell, and the function is damaged or even destroyed, which can cause serious clinical manifestations [16]. The severity of the clinical manifestations of hyponatremia depends on the rate of decline in Na^+ concentration. When blood Na^+ is above 125 mmol/L, it rarely causes symptoms; when Na^+ is between 125 - 130 mmol/L, gastrointestinal symptoms such as nausea and vomiting may be present [17]. The main systemic symptoms are weakness, nausea and vomiting, headache and drowsiness, painful muscle spasms, neuropsychiatric symptoms, and reversible ataxia. Early in the development of hyponatremia, brain cells adaptively regulate the intra- and extracellular osmolarity imbalance [18]. In normal pregnancy, an increase in β-human chorionic gonadotropin resets the arginine vasopressin (AVP) release penetration set point, which stimulates increased water intake and dilution of body fluids. Since the release of AVP is not inhibited at the typical level, the hormone continues to circulate and the intake of water is retained. In addition, the increase in estrogen and relaxin levels contributes to systemic vasodilatation, resulting in a decrease in systemic arterial blood pressure, and contributes to the release of AVP by non-permeable stimulation and thirst to stimulate placental trophoblast cells to produce vasopressin [19,20]. Other non-permeable stimulation of AVP secretion associated with pregnancy, such as nausea, vomiting, and pain, can stimulate AVP secretion and water retention. Oxytocin and AVP are released during uterine contraction, and oxytocin enhances the effect of AVP; in some cases, the use of synthetic oxytocin results in medically induced hyponatremia [8,21]. Hyponatremia in PE patients can cause ascites, pleural effusion, and pericardial effusion. In severe cases, pulmonary edema or heart failure can occur and further aggravate vasospasm, resulting in a vicious cycle of PE disease progression and aggravation of hyponatremia.

This study showed that 24-hour urinary protein and creatinine were independent risk factors for combined hyponatremia in PE. The interpretation and application of 24-hour urinary protein quantification in patients with severe PE have been controversial in recent years, and some international guidelines no longer use 24-hour urinary protein as a mandatory indicator for the diagnosis of severe PE due to its difficulty in collection, time-consuming testing, and the possibility of occult nephritis [22]. Quantitative 24-hour urinary protein testing in patients with PE is able to predict pregnancy outcome [23]. In this study, 24-hour urinary protein and uric acid simultaneously appeared significantly elevated in patients in the observation group, and logistics regression analysis also suggested that 24-hour urinary protein and uric acid were independent risk factors for the complication of hyponatremia in patients with PE. The higher the expression level of both, the higher the probability of PE combined with hyponatremia. However, at present, there are not many studies on the mechanism of 24 hour urinary protein and uric acid and the occurrence of hyponatremia in PE, and their pathological mechanisms are not yet very clear. We believe that the cause may be as follows: the pathological basis of PE is the systemic hypercoagulable state caused by systemic small vessel spasm and vascular endothelial injury. On the one hand, it can be reflected as the increase of 24-hour urinary protein and uric acid level caused by secondary hyperfibrinolysis [24,25]; on the other hand, another mechanism can be explained by iatrogenic oxytocin administration. Due to the molecular similarity between oxytocin and ADH, oxytocin acts on ADH receptors at the same time. Despite the fact that elevated ADH leads to hypovolemic hyponatremia, oxytocin still has a contributory effect in patients who develop hypervolemic hyponatremia [26,27]. Eventually, the combined effect of several links leads to the development of combined hyponatremia in patients with PE. Hyponatremia will further increase the exudation of tissue space, form a vicious circle, and aggravate the development of the disease. The present study suggested that 24-hour urinary protein and uric acid levels were clinically valuable in evaluating the development of hyponatremia in patients with PE in the later stages of the disease.

In conclusion, patients with PE combined with hyponatremia have a higher risk of maternal and fetal adverse outcomes. Detection of the urinary protein/creatinine ratio helps to assess the risk of developing combined hyponatremia in patients with PE, which helps us to predict the risk of patients with PE and to develop individualized treatment strategies for high-risk patients. In addition, patients with PE combined with hyponatremia may be a warning factor for the occurrence of preeclampsia, as a decrease in serum albumin levels can occur before proteinuria appears, with high sensitivity. The lower the serum albumin level, the more severe the condition of preeclampsia and the higher the incidence of complications. At present, there is no research on whether early correction of hypoproteinemia can reduce the incidence rate of preeclampsia. This study is the first to point out that the late pregnancy urinary protein/creatinine ratio is an independent risk factor for preeclampsia combined with hyponatremia. However, the main limitation of our study is the limited sample size. Further research should expand the sample to demonstrate our data.

Ethical Approval Statement:
All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were approved by Ganzhou Women and Children's Health Care Hospital (no. 201903GZ03).

Data Availability Statement:
Data is available from the corresponding author on request.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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