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Original article

# The significance of combined detection of CysC, urinary mAlb and $\beta_2$ -MG in diagnosis of the early renal injury in pregnancy-induced hypertension syndrome

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## ABSTRACT

**Objective:** To elaborate the significance of combined detection of cystatin C, urinary micro-albumin (mAlb) and  $\beta_2$ -microglobulin ( $\beta_2$ -MG) in diagnosis of the early renal injury in pregnancy-induced hypertension syndrome.

**Methods:** A total of 120 patients with pregnancy-induced hypertension syndrome who were admitted to this hospital for treatment between November 2015 and October 2018 were enrolled as subjects, and divided into the control group (without complication of renal injury, n = 76) and the observation group (with complication of renal injury, n = 44) according to the complications of early renal injury. Furthermore, 60 patients who participated in the antenatal care in this hospital were enrolled as the normal subjects (normal group). Automatic biochemistry analyzer was utilized to measure CysC, urinary mAlb and  $\beta_2$ -MG in serum to evaluate the specificity, sensitivity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of single or combined measurements of these indexes in diagnosis of the early renal injury in pregnancy-induced hypertension syndrome.

**Results:** In the observation group, the levels of CysC, urinary mAlb and  $\beta_2$ -MG were higher than those in the control group, while the levels in the normal group were the lowest ( $P < 0.05$ ). Combined measurement of CysC, urinary mAlb and  $\beta_2$ -MG showed a higher accuracy (90.0%) in diagnosis of the early renal injury in pregnancy-induced hypertension syndrome than the single measurements, and the difference had statistical significance ( $P < 0.05$ ). Besides, the sensitivity, specificity, PPV and NPV of the combined measurements were 94.59%, 87.30%, 81.40% and 94.49%, slightly higher than the single measurements, with no statistical significance in differences ( $P > 0.05$ ).

**Conclusion:** CysC, urinary mAlb and  $\beta_2$ -MG can reflect the renal injury effectively, and the combined measurements shows potent accuracy in diagnosis of the early renal injury in pregnancy-induced hypertension syndrome, thereby providing the scientific evidence for early diagnosis and stipulation of rational therapeutic regimen and improving the pregnancy outcome.

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## 1. Introduction

Pregnancy-induced hypertension syndrome is the specific disease of pregnant and lying-in women, with an incidence rate of about 5% to 12%, and also the major cause for the maternal and fetal death in developing country, resulting in the death of about 76,000 pregnant women and 500,000 fetuses or neonates (Cairns et al., 2016). Generally, pregnancy-induced hypertension

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syndrome develops at the 20th gestational week, and pathological changes involve the anomaly in coagulation and general arterial spasm, with clinical manifestations of hypertension, edema and proteinuria (Bi et al., 2013). Due to the increased oxygen consumption in kidney in pregnancy, inadequate perfusion or hypoxia results in the renal injury without any prompt intervention or therapy (Schoenaker et al., 2015). However, clinically, the early-stage renal injury in the pregnancy-induced hypertension syndrome is frequently ignored due to the lack of specific manifestation in the early stage, which endows the early diagnosis and treatment the great significance for maternal and fetal health. At present, blood urinary nitrogen, serum creatine (SCr) and glomerular filtration rate (GFR) have been extensively used for evaluation of renal function in clinical practice, but show a lower specificity in diagnosis due to the potent capability in storage of kidney, and the influences of medication, age, metabolism and muscle volume (Petrovic et al., 2016). Thus, we probed the effect of serum cystatin C, urinary micro-albumin (mAlb) and  $\beta_2$ -microglobulin ( $\beta_2$ -MG) in diagnosis of the early-stage renal injury in pregnancy-induced hypertension syndrome, thereby providing guidance and evidence for the diagnosis and treatment of this condition. Detailed information of this study is reported.

## 2. Data and methods

### 2.1. General data

A total of 120 patients with pregnancy-induced hypertension syndrome who were admitted to this hospital for treatment between November 2015 and October 2018 were enrolled as subjects, and divided into the control group (without complication of renal injury,  $n = 76$ ) and the observation group (with complication of renal injury,  $n = 44$ ) according to the complications of early renal injury. In the observation group, 44 patients had complications of the early-stage renal injury, aged from 23 to 37 years old, with an average of  $(28.14 \pm 5.96)$  years old; gestational weeks ranged from 22 to 38 weeks, with an average of  $(30.75 \pm 3.65)$  weeks; weight ranged from 58.86 to 79.76 kg, with an average of  $(69.14 \pm 4.54)$  kg. In the control group, 76 patients had no complications of the early-stage renal injury, aged from 22 to 38 years old, with an average of  $(29.96 \pm 6.14)$  years old; gestational weeks ranged from 23 to 38 weeks, with an average of  $(31.27 \pm 3.46)$  weeks; weight ranged from 59.13 to 78.10 kg, with an average of  $(68.94 \pm 4.10)$  kg. Simultaneously, another 60 healthy pregnant women who attended the antenatal care in this hospital were enrolled as the normal group. In the normal group, subjects aged from 21 to 39 years old, with an average of  $(28.48 \pm 6.85)$  years old; gestation weeks ranged from 23 to 39 weeks, with an average of  $(30.76 \pm 3.83)$  weeks; weight ranged from 59.86 to 79.15 kg, with an average of  $(69.37 \pm 4.66)$  kg. The general data, including the age, gestation weeks and weight, of the subsection among three groups were in normal distribution, and the differences among three groups showed no statistical significance ( $P > 0.05$ ), suggesting that the data were comparable. The protocol was reviewed and approved by the Ethic Committee of the hospital.

### 2.2. Inclusion and exclusion criteria

#### 2.2.1. Inclusion criteria

All patients conformed to the diagnostic criteria of pregnancy-induced hypertension syndrome in the *Obstetrics and Gynecology* (8th edition), and diagnoses were further confirmed through the clinical symptoms, blood pressure and regular physical examination. All subjects aged between 18 and 40 years old and were all primiparae, with single birth; all subjects had signed the written

informed consents after they were sufficiently informed of the content of this study.

#### 2.2.2. Exclusion criteria

Patients with the history of primary hypertension, diabetes mellitus, renal diseases or severe anemia, or complications of other pathological pregnant diseases, or the cardiovascular or endocrine diseases, or who had the drugs that might affect the renal functions were excluded from this study.

### 2.3. Methods

In the morning, 5 mL of fasting venous blood was collected from all subjects for centrifugation at 3500 r/min for 5 min to isolate the serum which was preserved at  $-80^\circ\text{C}$  for later use. Latex-enhanced immunoturbidimetry was applied to determine the level of CysC in serum, while immunoturbidimetry to determine the level of  $\beta_2$ -MG, with the Hitachi 7170 Automatic Biochemical Analyzer and the kits provided from Beijing Wantai DRD Co., Ltd. Besides, urine was collected in the morning from the subjects to detect the level of mAlb in urine by using the immunity transmission turbidity, with the Hitachi 7170 Automatic Biochemical Analyzer and the kits provided from the Ningbo Ruiyuan Biotechnology Co., Ltd. All experiments were conducted in accordance with the instructions.

### 2.4. Observation index

We compared the levels of CysC, urinary mAlb and  $\beta_2$ -MG among three groups, and evaluated the specificity, sensitivity, accuracy, positive prediction value (PPV) and negative prediction value (NPV) in single or combined measurements of these indexes, with the clinical diagnosis as the golden criteria. Early-stage renal injury was deemed as positive, and no early-stage renal injury as negative, a as true positive, d as true negative, c as false positive and b as false negative. Accuracy =  $(a + d)/n$ , sensitivity =  $a/(a + c)$ , and specificity =  $d/(b + d)$  (Risch et al., 2001). Positive results were evaluated according to the following criteria: CysC  $> 1.12$  mg/L, urinary mAlb  $> 30$  mg/L, and  $\beta_2$ -MG  $> 1.58$  mg/L (Fliser and Ritz, 2001).

### 2.5. Statistical analysis

All data were integrated into the Excel to establish the database for following analysis in SPSS 22.0 software. Measurement data in form of mean  $\pm$  standard deviation were compared by using the *t* test. Enumeration data in form of frequency or rate were compared by chi-square test. Difference with  $P < 0.05$  suggested the statistical significance.

## 3. Results

### 3.1. Levels of CysC, urinary mAlb and $\beta_2$ -MG

In the observation group, the levels of CysC, urinary mAlb and  $\beta_2$ -MG were higher than those in the control group, while the levels in the normal group were the lowest ( $P < 0.05$ ; Table 1).

### 3.2. Comparison of the single or combined measurements of CysC, urinary mAlb and $\beta_2$ -MG

Combined measurement of CysC, urinary mAlb and  $\beta_2$ -MG showed a higher accuracy (90.0%) in diagnosis of the early renal injury in pregnancy-induced hypertension syndrome than the single measurements ( $P < 0.05$ ; Table 2–5).

**Table 1**

Comparison of the levels of CysC, urinary mAlb and  $\beta_2$ -MG among three groups (mg/L,  $\bar{x} \pm s$ ).

Group	n	CysC	Urinary mAlb	$\beta_2$ -MG
Normal group	60	0.82 $\pm$ 0.20	12.75 $\pm$ 4.11	1.16 $\pm$ 0.28
Control group	76	1.17 $\pm$ 0.33	16.51 $\pm$ 5.62	1.47 $\pm$ 0.48
Observation group	44	1.88 $\pm$ 0.86	35.08 $\pm$ 8.85	3.24 $\pm$ 1.20
F		78.762	57.874	61.724
P		0.000	0.000	0.000

**Table 2**

Comparison between the results of CysC and pathological test (n).

CysC	Pathological test		Total
	Positive	Negative	
Positive	36	16	52
Negative	8	60	68
Total	44	76	120

**Table 3**

Comparison between the results of urinary mAlb and pathological test (n).

Urinary mAlb	Pathological test		Total
	Positive	Negative	
Positive	35	17	52
Negative	9	59	68
Total	44	76	120

**Table 4**

Comparison between the results of  $\beta_2$ -MG and pathological test (n).

$\beta_2$ -MG	Pathological test		Total
	Positive	Negative	
Positive	33	19	52
Negative	11	57	68
Total	44	76	120

**Table 5**

Comparison between the results of combined measurements of CysC, urinary mAlb and  $\beta_2$ -MG and pathological test (n).

Combined measurements	Pathological test		Total
	Positive	Negative	
Positive	42	10	52
Negative	2	66	68
Total	44	76	120

### 3.3. Comparison of the sensitivity, specificity, PPV and NPV of the single or combined measurements of CysC, urinary mAlb and $\beta_2$ -MG in diagnosis of the early-stage renal injury in pregnancy-induced hypertension syndrome

Besides, the sensitivity, specificity, PPV and NPV of the combined measurements were 94.59%, 87.30%, 81.40% and 94.49%, slightly higher than the single measurements, with no statistical significance in differences ( $P > 0.05$ ; Table 6).

## 4. Discussion

It has been reported that pregnancy-induced hypertension, or the complications of heart disease or postpartum hemorrhage are the major causes for maternal death (Qi and Anand, 2015). Pathological changes mainly involve the injury of the vascular endothe-

**Table 6**

Efficiency of the single or combined measurements of CysC, urinary mAlb and  $\beta_2$ -MG in diagnosis.

Items	Sensitivity	Specificity	Accuracy	PPV	NPV
CysC	81.07	79.36	80.00	69.76	87.71
Urinary mAlb	78.37	77.77	78.00	67.43	85.95
$\beta_2$ -MG	72.96	74.59	74.00	62.78	82.45
Combination	94.58	87.29	90.00	81.39	94.48
$\chi^2$	6.298	3.418	8.856	3.875	5.841
P	0.097	0.331	0.030	0.274	0.119

lial cells and inflammatory responses in vascular system that may induce the spasm of small vessels. As one of the major organs for blood pressure regulation, kidney is also one of the target organs affected by the hypertension, and the injury of renal function may exacerbate the hypertension, thereby forming a vicious cycle, aggravating the damage to the key organs and resulting in the renal dysfunction (Shah and Khalil, 2015). Hence, it is quite important to develop the more sensitive detection items for the diagnosis and intervention of early-stage injury in pregnancy-induced hypertension syndrome.

CysC, as one of the basic, non-glycosylated protein consisting of 122 amino acids, is usually in the constant and stable synthesis and transcription in the karyocytes of human (including insulin cells, thyroid cells and nerve cells) and secreted in the kidney, with advantages of positive charges, small molecular weight and no tubular secretion. CysC can be directly delivered through the basal membrane of the glomeruli, without being affected by the malignancy, inflammation, age or other factors, keeps stable in serum and is metabolized and reabsorbed by the proximal convoluted tubule (Herget et al., 2000; Risch et al., 2001). For the level of CysC in serum depends on the GFR, CysC can be used as the indicator of the lesions in the permeability of glomerulus filtration (Fliser and Ritz, 2001). Renal injury, concomitant with a decrease in the GFR, usually results in the rapid increase of CysC level in serum. Thus, CysC level is positive correlated with the injury of glomerulus and disease progression (Paskalev et al., 2001).

Generally, urinary mAlb can hardly pass through the charge barrier and the basal membrane of glomerulus, and the secreted albumin is usually within 10 and 30 mg/d (Ninomiya et al., 2009). Due to the involvement of renal vessels in the hypertension, and the influences of high perfusion, capillary sclerosis, vascular endothelial injury, dysfunction of filtration barrier and anomaly in the basal membrane of glomerulus, the permeability of vascular wall in glomerulus is enhanced, with damage to the filtration membrane and the resultant decrease of the negative charge and electrostatic repulsive-force, resulting in the increase in urinary mAlb level (Gosmanova et al., 2014; Ranque et al., 2014). Recently, urinary mAlb has been clarified as an independent predictive factor of the hypertension, cardiovascular complications and other chronic renal diseases, and also one of the reliable and sensitive indicators of the early-stage renal injury (Bartolucci et al., 2015). According to the clinical study, disease progression can be retarded by the reversal therapy to mitigate the renal injury.

$\beta_2$ -MG, a protein in a relative molecular weight of 11,800, is mainly produced by the human lymphocytes, and serves as a sensitive indicator of the glomerular filtration rate and the reabsorption function of the proximal tubule that reflects the renal injury (Mattes and Walker, 2009; Vaidya, 2010a, 2010b). Physiologically, release and synthesis of the  $\beta_2$ -MG are constant, and 99.9% of  $\beta_2$ -MG is reabsorbed and filtrated by the glomerulus, resulting in a relatively lower level in serum. Decreased function of reabsorption of the tubule by any injury of the tubular functions can result in the release of free  $\beta_2$ -MG in serum, further resulting in an obvious increase (Sistare, 2010; Vaidya, 2010a, 2010b).

In this study, in the observation group, levels of CysC, urinary mAlb and  $\beta_2$ -MG exceeded those of the control group, while the levels in the normal group were the lowest; furthermore, the accuracy of the combined measurements was higher in predicting the early-stage renal injury in pregnancy-induced hypertension syndrome, while the sensitivity, specificity, PPV and NPV were only slightly higher than the single measurement. Thus, combined measurements of CysC, urinary mAlb and  $\beta_2$ -MG are advised in clinical diagnosis of the early-stage renal injury in pregnancy-induced hypertension syndrome, so as to increase the prediction efficiency.

## 5. Conclusion

In conclusion, CysC, urinary mAlb and  $\beta_2$ -MG can reflect the renal injury effectively, and the combined measurements shows potent accuracy in diagnosis of the early renal injury in pregnancy-induced hypertension syndrome, thereby providing the scientific evidence for early diagnosis and stipulation of rational therapeutic regimen and improving the pregnancy outcome.

## Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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## Further reading

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