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Evaluation of the predictive value of high sensitivity C-reactive protein in pregnancy-induced hypertension syndrome

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Abstract. Relationship between serum high sensitive C-reactive protein (hs-CRP) and pregnancy-induced hypertension syndrome (PIH) was investigated. One hundred and twenty patients with PIH treated in the First People's Hospital of Chengdu (60 cases of mild preeclampsia, 60 cases of severe preeclampsia) were enrolled in the study. The control group included 60 women with normal singleton pregnancy. Serum hs-CRP and microalbuminuria (mALB) levels were measured by an AU5800 automatic biochemical analyzer (Beckerman Coulter), and the risk factors were analyzed by ROC curve analysis. Patients with PIH had higher levels of serum hs-CRP and mALB than the control group (P<0.01). Serum hs-CRP and mALB levels in the severe preeclampsia group were significantly higher than those in the mild preeclampsia group (P<0.05). ROC curve analysis showed that hs-CRP was a factor of high-risk. Area under the curve was 0.943, and the 95% confidence interval was 0.848-0.974. Detection of serum hs-CRP in patients with PIH can provide references for the prediction of the severity of the disease, and higher level of hs-CRP indicates worse condition.

Introduction

Pregnancy-induced hypertension syndrome (PIH) (1) is an idiopathic disease prone to occur in late pregnancy. At present, incidence of PIH in China is approximately 10%, and has become the most common serious complication of pregnancy. PIH as one of the top 3 leading causes of death in pregnant women seriously affecting maternal and infant health and safety (1-4). Clinical manifestations of PIH include edema, hypertension and urinary protein (5,6). Intervention in the early phase can effectively prevent the occurrence of severe symptoms. Microalbuminuria (mALb) is a macromolecule protein that can be used as a marker for early glomerular injury (7). C-reactive protein (CRP) is a non-specific inflammatory-related protein produced by the liver and regulated by plasma interleukin-6 (IL-6) (8). Qiu *et al* (9) discovered that serum CRP was significantly elevated in patients with PIH. Another study showed that postpartum PIH patients had higher levels of high sensitivity CRP (hs-CRP) than non-PIH patients (10). The goal of this study was to investigate the predictive value of serum hs-CRP for PIH patients and to explore its clinical diagnostic value.

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Patients and methods

Patient information. PIH patients treated in The First People's Hospital of Chengdu from June 2013 to December 2015 were selected into this study. Among them, 60 patients had mild preeclampsia and the other 60 had severe preeclampsia. Sixty women with normal pregnancy during the same time period were included as control group. The PIH patients had varying degrees of edema, headache, high blood pressure, blurred vision; and their symptoms were in accordance with the PIH diagnostic criteria. Patients with tumors, blood diseases, essential hypertension, contagious diseases and severe liver and kidney diseases were excluded. Patients were divided into three groups: mild preeclampsia group, severe preeclampsia group and normal control group. Patients in the PIH group were aged from 22 to 43 years, and the average was 26.7±8.4 years, and they had given 1-3 births, and the average age was 2.4±0.6. Their gestational ages were 32-41 weeks, and the mean was 32.4±4.1 weeks. Patients in the control group were aged from 20 to 47 years, and the mean age was 25.7±8.1 years, and they had given 1-3 births, and the average was 2.1±0.5. Their gestational ages were 32-41 weeks, and the average was 33.6±3.7 weeks. There were no significant differences in age, number of previous birth and gestational age between the two groups (P>0.05). All pregnant women and their families were informed and signed the informed consent. This study was approved by the Ethics Committee of The First People's Hospital of Chengdu (Chengdu, China).

Inclusion and exclusion criteria. Inclusion criteria: Patients had not recently received irritant drug treatment, patients without family genetic disease, patients without memory and hearing impairment, patients who cooperated with follow-up and patients with compete clinical record.

Table I. Comparisons of clinical data of the three groups (mean ± standard error).

Group	Mild preeclampsia (n=60)	Severe preeclampsia (n=60)	Control (n=60)	F-value	P-value
Age (years)	27.1±7.4	26.8±7.9	25.7±8.1	0.535	0.587
Gestational age (weeks)	32.7±4.5	32.1±4.7	33.6±3.7	1.831	0.163
No. of births (n)	2.3±0.7	2.5±0.5	2.3±0.6	2.182	0.116
Fasting blood glucose (mmol/l)	5.2±0.6	5.1±0.5	5.2±0.4	0.779	0.460
Na^+ (mmol/l)	140.7±4.8	143.1±5.4	142.5±5.2	1.121	0.328
K^+ (mmol/l)	4.2±0.5	4.3±0.7	4.2±0.6	0.546	0.581
Total cholesterol (mmol/l)	4.8±0.8	4.7±0.6	4.7±0.9	0.332	0.718
Triglycerides (mmol/l)	1.6±0.8	1.7±0.7	1.6±0.8	0.339	0.713

Table II. Comparison of hs-CRP and mALb in peripheral blood among 3 groups (mean ± standard error).

Group	n	hs-CRP (mg/l)	mALb (mg/l)
Control	60	2.1±1.2	6.4±4.1
Mild preeclampsia	60	3.3±0.7[a]	30.6±6.3[a]
Severe preeclampsis	60	5.4±1.6[a]	35.4±4.2[a]

Expression of hs-CRP and mALb in patients with mild preeclampsia and severe preeclampsia were detected and the expression levels were higher than those in the control group ([a]P<0.05). hs-CRP, high sensitive C-reactive protein; mALb, microalbuminuria.

Exclusion criteria: Patients below 18 years, patients with respiratory system disease, patients with blood relationship with other patients, patients who recently received blood transfusion therapy, patients with mental disease or physical insufficiency.

Diagnostic methods. Diagnostic methods refer to the 'Chinese Hypertension Prevention Guidelines' (11). Diagnostic criteria for PIH patients: blood pressure ≥140/90 mmHg after 20 weeks of pregnancy, and patients with urine protein ≥0.3 g/24 h or positive random urine protein, clinical manifestations of abdominal discomfort, headaches and other symptoms. Severe patients with blood pressure ≥160/110 mmHg, urinary protein ≥2.0 g/24 h or a strong positive random urine protein, serum creatinine >1,061 μmol/l, platelets <100x10^9/l, micro-angiopathic hemolysis (blood LDH elevating), stent headaches or other neurological or visual disturbances and persistent epigastric discomfort.

Methods. A total of 3 ml of intravenous blood was extracted from the PIH patients in the morning and stored in test tubes with anticoagulant. Fasting blood was obtained from the patients in the control group during their regular checkups. Level of hs-CRP in blood was measured by immunosorbent assay. Morning urine (3 ml) was collected to measure levels of mALb by immunoturbidimetry. hs-CRP and mALb kits were provided by Beijing Strong Biotechnology Co., Ltd. (Beijing, China). All tests were carried out by using Beckman Kurt AU5800 automatic biochemical analyzer. Standards and controls were provided by the manufacturers, and all operations were performed in strict accordance with the manufacturer's instructions.

Statistical analysis. SPSS 20.0 statistical software (IBM SPSS, Armonk, NY, USA) was used for data analysis. Measurement data were expressed as mean ± standard error and underwent normal distribution test. Non-normal distribution data were converted to normal distribution data before comparisons. ANOVA analysis was used for the comparisons among multiple groups and the post hoc test was Dunnett's test. ROC curve was used to analyze the predictive value of hs-CRP for PIH. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of clinical data. Clinical data of three groups of patients were compared. Results showed no significant differences in age, gestational age, number of birth, fasting blood glucose, electrolytes, and blood lipids among 3 groups (P>0.05) (Table I).

Comparison of the levels of hs-CRP and mALb. Compared with the control group, the mild preeclampsia group and the severe preeclampsia group showed significantly higher hs-CRP and mALb levels (P<0.05). There were significant differences in levels of hs-CRP and mALb between the two preeclampsia groups (P<0.05) (Table II).

Analysis of diagnostic value of hs-CRP for PIH by ROC curve analysis. Potential diagnostic value of hs-CRP for PIH was analyzed by using ROC curve analysis. Results showed that hs-CRP had high predictive value for PIH with an AUC of 0.943 and 95% confidence interval (CI): 0.848-0.974. These data suggested that hs-CRP can be used as a potential diagnostic marker for PIH (Fig. 1).

Discussion

PIH is a unique disease in pregnant women that mainly affects women after 20 weeks of gestation and/or two weeks postpartum. Major symptoms include protein in urine and hypertension, and PIH occurs in 5% of pregnant women (12).

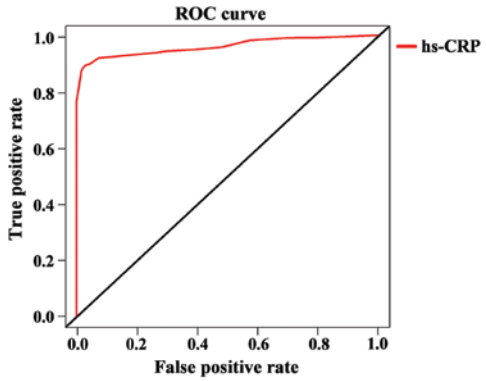

Figure 1. ROC curve analysis of the diagnostic value of hs-CRP. ROC curve analysis showed that area under the curve (AUC) was 0.943 with 95% CI of 0.848-0.974, specificity of 78.5% and sensitivity of 88.7%. Therefore, hs-CRP may serve as a potential diagnostic biomarker. hs-CRP, high sensitive C-reactive protein; CI, confident interval.

Studies have shown that (9) PIH not only cause serious complications during perinatal period, but also increase the incidence of cardiovascular and cerebrovascular diseases, seriously affecting the health and safety of pregnant women.

Currently, it is thought that inflammatory response may participate in the occurrence and development of PIH, and PIH may be the first step of the onset of cardiovascular disease in women (13). Clinically, PIH is primarily diagnosed by quantification of 24 h urine protein and monitoring blood pressure, but those two indicators are susceptible to other factors (14). Increasing number of studies have shown that CRP plays an important role in the occurrence and development of PIH. CRP as an acute phase reaction protein is synthesized in liver cells, and detection of hs-CRP is more sensitive than CRP. hs-CRP is a sensitive marker reflecting low-level inflammation, and it is specifically expressed in cardiovascular disease (10). hs-CRP is an indicator for atherosclerosis, and is also one of the risk factors for hypertension. In a serum of healthy people, hs-CRP content is low, while its level increases dramatically in non-infectious inflammation (15). PIH occurs through systemic arteriolar spasms. The underlying mechanism is the injury and activation of endothelial cells, which causes placental ischemia and hypoxia. With those pathological changes, a series of cytotoxic factors will be released into the maternal body and lead to increased intravascular permeability. Finally, PIH patients will show prethrombotic symptoms and excessive coagulation substances will be released, which in turn lead to elevated blood hs-CRP level (16,17).

In this study, we investigated the expression of hs-CRP and clinical data of 120 patients with PIH and 60 normal pregnant women. The results showed that there were no significant differences among the three groups in clinical data, indicating that fasting blood glucose, electrolytes and lipids have no obvious impact on PIH. However, significant differences in peripheral blood hs-CRP and mALb were found between preeclampsia patients and normal pregnant women, and their levels increased when the eclampsia became more severe. These two indicators could be used as markers for the diagnosis of PIH. A study showed that (18) PIH patients had significantly higher mALb level than pregnant women without PIH, and elevated mALb excretion proceeded other clinical manifestations. Another study by Ertas *et al* (19) showed that e treatment of PIH patients. Finally, ROC curve analysis showed that hs-CRP had an AUC =0.943 and 95% CI: 0.848-0.974 in the diagnosis of PIH, which suggested that hs-CRP can be used to effectively predict PIH. Wang *et al* (20) suggested that hs-CRP can be used as a standard for the diagnosis of PIH, which is consistent with our conclusions.

ROC curve analysis used in this study increased the reliability of our data. However, there are still some drawbacks. The small sample size and regional differences might lead to bias of our results. Moreover, this is only a clinical study and no further study was performed. Therefore, more studies with larger sample size are needed to confirm the conclusions in the future.

In conclusion, peripheral blood hs-CRP increased with the development of PIH, and it could be used as a potential diagnostic marker for PIH. Monitoring hs-CRP closely can effectively control the development of this disease and timely intervene, which can effectively inhibit the progression of disease. Sufficient attention should be paid to its clinical value.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HC drafted and finalized this manuscript. JZ and FQ were devoted to collecting and interpreting the data. XC and XJ revised it critically for important intellectual content. HC, JZ, FQ, XC and XJ contributed to the conception and design of the study. All authors read and approved the final study.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The First People's Hospital of Chengdu (Chengdu, China). Signed informed consents were obtained from the patients or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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