• Clinical Research •

A algorithm for prediction of exudative retinal detachment risk of patients with pregnancy-induced hypertension

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Abstract

● **AIM:** To investigate the risk of exudative retinal detachment (ERD) morbidity in patients with pregnancy-induced hypertension (PIH) by using the logistic regression combined with the receiver operating characteristic (ROC) curve.

● **METHODS:** A total of 46 patients with ERD and 142 patients with non-ERD were diagnosed as PIH from January 2017 to February 2020. A retrospective comparison of the clinical manifestations and laboratory tests were conducted. The risk of ERD morbidity with PIH was predicted by using logistic regression combined with an ROC curve model.

● **RESULTS:** There was no significant difference in age and body mass index between the two groups before pregnancy ($P>0.05$). However, significant differences were found in gestational weeks, duration of hypertension, maximum and minimum systolic and diastolic blood pressure (BP), and plasma total protein (PTP) concentration between the two groups ($P<0.05$). Binary logistic regression analysis showed that the maximum systolic BP (OR=1.050, 95%CI: 1.016-1.085) and PTP concentration (OR=0.764, 95%CI: 0.702-0.832) were independent prediction risks of ERD in PIH. The sensitivities of maximum systolic BP, PTP concentration and combined diagnosis were 0.717, 0.870, and 0.870, respectively; the specificities were 0.617, 0.837, and 0.908, respectively; the area under the curve (AUC) was 0.707 (95%CI: 0.622-0.792), 0.917 (95%CI: 0.868-0.967), and 0.933 (95%CI: 0.890-0.975), respectively; the AUC of combined diagnosis was higher than that of single diagnosis ($P<0.01$).

● **CONCLUSION:** Logistic regression and ROC curve model combined with maximum systolic BP and PTP can improve the early identification of high-risk PIH patients in the hospital.

INTRODUCTION

Pregnancy-induced hypertension (PIH) is one of the most common obstetric diseases, an unresolved and unpreventable problem in obstetrics, which remains the leading risk on the health life of mother and infant[1-2]. PIH causes a variety of pathological vascular changes, subsequently damages the function of most of all organs, such as liver, heart, renal, brain, and eye.

It is the only one vascularity of retina which could be directly seen in the whole body. The vascular pathological changes of retina caused by PIH are considered as the ominous signs to value the progress and prognosis of PIH.

Pregnancy can induce retinal diseases or aggravate the original retinal diseases[3], a composite of severe maternal outcomes, including maternal near-miss defined by World Health Organization, cortical blindness, retinal detachment, temporary facial paralysis and maternal death, were adopted[4].

The common fundus changes include retinal artery spasm, high retinal artery reflection, arteriovenous cross indentation, retinal hemorrhage, optic disc edema, chorioretinitis[5] and exudative retinal detachment (ERD). Optical coherence tomography (OCT) manifestations retinal neuroepithelial detachment, retinal pigment epithelium (RPE) detachment and ellipsoid band change[6-7].

ERD is the main cause of blurred vision in PIH patients, with the incidence of 0.1%-2% worldwide[8-11]. Fluorescence angiographic findings support the hypothesis that retinal detachment in pre-eclampsia is secondary to choroidal ischemia from intense arteriolar vasospasm[12-13]. The happening of the ERD could mean a higher risk of core outcomes: stillbirth, small gestational age at delivery, lower birthweight,

cardiovascular disease, neonatal mortality, seizures, admission to neonatal unit required and respiratory support[14-15]. Although most patients with ERD have good visual prognosis, but some patients have sustained damage in RPE layer and ellipsoid zone, which can lead to permanent loss of visual function in severe cases[16]. Therefore, identifying and intervening the risk factors related to ERD in pregnancy with hypertension can effectively reduce the abnormal pregnancy rate.

However, there is little knowledge on the risk factors of ERD in PIH patients. Here we conducted a retrospective study on the risk factors in PIH patients and found a significant correlation between the accidence of ERD and blood pressure (BP) and total protein concentration. Then we formed an algorithm with BP and total protein concentration to predict the accidence of ERD, which may extent more time before ERD and other hidden troubles occurring in PIH patients.

SUBJECTS AND METHODS

Ethical Approval The study was conducted in accordance with the Declaration of Helsinki and all the patients signed the informed consent.

From January 2017 to February 2020, 188 patients with PIH hospitaled in the Obstetrics Department of the Third Affiliated Hospital of Guangzhou Medical University, were enrolled and divided into two groups according to the results of fundus examination, namely, 46 ERD cases (ERD group) and 142 non-ERD ones (non-ERD group).

Best corrected visual acuity (BCVA) of 188 patients ranged from 0.1 to 1.0, with an average of 0.59±0.18. The diagnostic criteria for ERD were retinal neurodermis detachment, which was detected by fundus photography, retinal prescopy, and OCT. At the same time, the retinal detachment caused by tear and pull factor was excluded. Patients with ERD in one eye or more were enrolled to the ERD group. ERD fundus photography and OCT were shown in Figures 1 and 2.

The exclusion criteria were as follows: 1) the fundus photography and OCT examination were not completed; 2) with previous retinal and choroidal diseases; 3) the patients suffered from other conditions which could damage the retina, such as high myopia, diabetes, uremia, thrombocytopenic purpura, syphilis, dengue fever, and infection[17].

All patients were asked if there were blurred vision and dark shadow in front of their eyes. The common data of them, including age, gestational weeks, duration of hypertension, past medical history, pre-pregnancy body mass index (BMI) were recorded. And then, every case underwent 24-hour ambulatory BP monitor and the maximum systolic and diastolic BP were determined by measurement results. Visual acuity, fundus examination, fundus photography, and OCT examination were conducted by the senior ophthalmologist. Plasma total protein (PTP) concentration were also collected. The plasma colloid osmotic pressure[18] was calculated as following: plasma colloid osmotic pressure (PCOP, mm Hg)=2.1×PTP concentration (g/dL)+0.16×PTP concentration^2(g/dL)+0.009×PTP concentration^3(g/dL).

Statistical Analysis Statistical analysis was performed using SPSS 16.0. The data were described by mean±standard deviation and median (interquartile interval) [M (P25, P75)], and compared between groups by independent sample t-test and Mann-Whitney U nonparametric test. Binary Logistic regression Rorward: LR method were used to value and sieve the potential risk factors of ERD in PIH patients. Receiver operating characteristic (ROC) curve was used to test the prediction and diagnostic efficiency of the algorithm.

RESULTS

There was no significant difference in age and pre-pregnancy BMI between ERD group and non-ERD group ($P>0.05$). Nevertheless, there were statistically significant differences in gestational weeks, duration of hypertension, maximum and minimum systolic and diastolic BP, and PTP concentration between two groups ($P<0.05$; Table 1).

The variables (gestational weeks, duration of hypertension, PTP concentration, maximum and minimum systolic and diastolic BP) which had statistical differences between two groups were analyzed by binary logistic regression analysis. The results showed that the maximum systolic BP and PTP concentration were statistically correlated with the occurrence of ERD (Table 2).

ROC curve analysis showed that the sensitivities of maximum systolic BP, total protein concentration and combined diagnosis were 0.717, 0.870, and 0.870, respectively; the specificities were 0.617, 0.837, and 0.908, respectively; the area under the curve (AUC) was 0.707 (95%CI: 0.622-0.792), 0.917 (95%CI: 0.868-0.967), and 0.933 (95%CI: 0.890-0.975), respectively. The AUC of combined diagnosis was higher than that of single diagnosis ($P<0.01$; Table 3, Figure 3).

DISCUSSION

As is known to all, there are two kinds of blood retinal barrier in normal retina to keep retina dry and transparent, *i.e.*, inner retinal barrier and outer retinal barrier. The inner retinal barrier is formed by the occlusive zone between the retinal capillary endothelial cells and the pericytes, the outer retinal barrier is composed of the RPE cell and its occlusive zone. When the RPE barrier is damaged, choroidal plasma leaks into the sub-neuroepithelial layer and accumulates in the neuroendothelial layers, then it forms a localized, well-defined, flat discoid retinal detachment, if the RPE barrier is extensively damaged, it may cause wide and highly uplifted ERD[19]. It is common in malignant hypertension[20], Harada disease[21], central serous chorioretinopathy[22], choroidal tumor[23], uveal effusion syndrome[24], posterior scleritis[25]. PIH is associated with
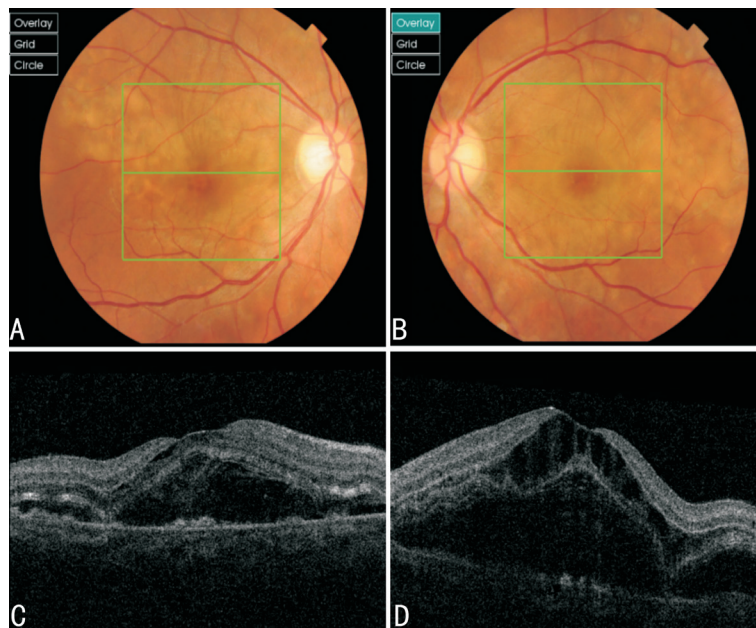
Figure 1 Fundus photography showed that the retina was edema and bulging. OCT suggested detachment and edema of the neuroepithelium A, B: Fundus imaging results of right and left eyes of case 1; C, D: OCT results of right and left eyes of the patient.
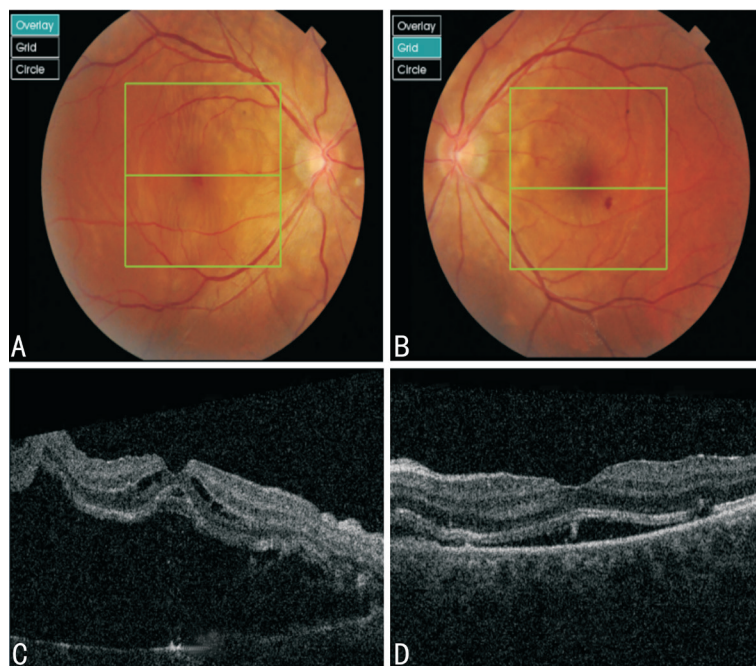

Figure 2 Fundus imaging suggested retinal edema, retinal eminence and hemorrhage. OCT suggested detachment and edema of the neuroepithelium A, B: Fundus imaging results of right and left eyes of case 2; C, D: OCT results of right and left eyes of the patient.

severe damage to choroidal circulation, which is generally believed to be caused by extensive destruction of the retinal barrier[10].

ERD is a serious complication of PIH and characterizes by the accumulation of serous or haemorrhagic fluid in the subretinal space secondary to hydrostatic factors. The retina is separated from the RPE beneath it and vision is lost because photoreceptors require contact with the RPE and choroid for metabolic and vascular support. Although most ERD resolves by clinical management after delivery 2 to 12wk[26-27], the symptoms caused by ERD, such as blurred vision, dark shadow in front of the eyes, and permanent visual loss may be left in a small number of PIH patients and seriously affected the their normal life. Arab *et al*[28] found that peripapillary retinal nerve fiber layer reduced in preeclamptic and eclamptic cases as well as in normotensive pregnant women at 2mo postpartum. This reduction was more in the severe forms of PIH. Meanwhile, offspring of mothers with hypertensive disorders during pregnancy have increased risk of cardiovascular disease[29]. Higher maternal BP during pregnancy is associated with

Table 1 Comparison of general data between ERD group and non-ERD Group   mean±SD; M (P25, P75)

Parameters	ERD group	Non-ERD group	Test value (*t/Z*)	*P*
Age (y)	32.41±5.13	32.08±5.19	-0.382	0.703
Gestational weeks	30.95 (28.08, 35.08)	35.35 (31.25, 37.30)	-3.269	0.001
Pre-pregnancy BMI (kg/m^2)	22.55 (19.45, 24.14)	22.83 (20.55, 24.63)	-1.315	0.188
Duration of hypertension (d)	3.00 (1.00, 7.50)	7.00 (1.50, 16.00)	-2.593	0.010
Max systolic BP (mm Hg)	170.00 (154.50, 180.50)	155.00 (148.00, 168.25)	-4.260	0.000
Min systolic BP (mm Hg)	145.00 (136.75, 155.00)	139.00 (127.00, 145.00)	-3.421	0.001
Max diastolic BP (mm Hg)	110.00 (101.50, 120.00)	100.00 (95.00, 107.00)	-4.467	0.000
Min diastolic BP (mm Hg)	93.50 (85.75, 101.25)	89.00 (80.00, 94.00)	-3.382	0.001
PTP concentration (g/L)	47.28 (43.38, 51.05)	62.39 (57.18, 66.37)	-8.491	0.000

BMI: Body mass index; BP: Blood pressure; PTP: Plasma total protein; ERD: Exudative retinal detachment.

Table 2 Logistic regression analysis of variables with statistical difference between two groups

Parameters	B	S.E.	Wald	df	*P*	Exp(B)	95%CI for Exp(B)
Max systolic BP	0.049	0.017	8.484	1	0.004	1.050	1.016-1.085
PTP concentration	-0.269	0.044	38.274	1	0.000	0.764	0.702-0.832
Constant	5.456	3.158	2.985	1	0.084	234.219	

BP: Blood pressure; PTP: Plasma total protein; S.E.: Standard error; df: Degree of freedom; Exp(B): OR value.

Table 3 Comparison of the efficacy of maximum systolic BP, PTP concentration and their combination in the diagnosis of ERD

Variable	AUC	Sensitivity	Specificity	Cut-off value	95%CI	*P*
Max systolic BP	0.707	0.717	0.617	159.5	0.622-0.792	0.000
PTP concentration	0.917	0.870	0.837	54.42	0.868-0.967	0.000
Combined diagnosis	0.933	0.870	0.908	8.714	0.890-0.975	0.000

BP: Blood pressure; AUC: Area under the curve; ERD: Exudative retinal detachment; PTP: Plasma total protein. The value of the combined diagnosis=(maximum systolic pressur–plasma colloid osmotic pressure)/plasma colloid osmotic pressure. Plasma colloid osmotic pressure (mm Hg)=2.1×PTP concentration (g/dL)+0.16×PTP concentration^2(g/dL)+0.009×PTP concentration^3(g/dL).
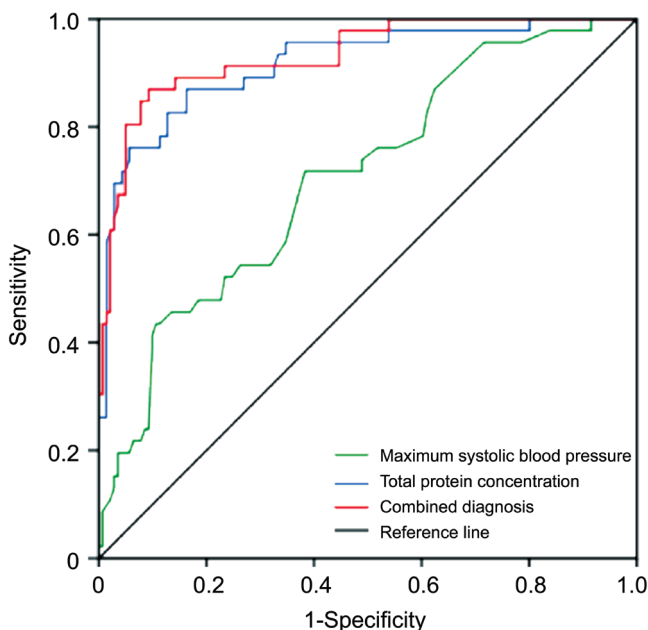

Figure 3 ROC curve of maximum systolic blood pressure, PTP concentration and combined variable in diagnosis of ERD PTP: Plasma total protein; ROC: Receiver operating characteristic; ERD: Exudative retinal detachment.

persistent microvasculature adaptations in their children. Children of mothers with gestational hypertensive disorders tended to have narrower retinal arteriolar caliber[30]. The destruction of micro-circulation in retina reflects the deterioration of micro-circulation in the other organs. The occurrence of ERD also means the requirement to terminate pregnancy in timely for preventing further damage of multiple organs. Thereby, early prediction of ERD is particularly important and may earn more time for preventing the further damage of the multiple organs before ERD and other hidden troubles occurring in PIH patients.

In the study, independent sample *t* test and Mann-Whitney *U* nonparametric test were used to compare gestational weeks, duration of hypertension, maximum and minimum systolic and diastolic BP, and PTP concentration between ERD group and non-ERD group. The results showed significant difference in maximum/minimum systolic and diastolic BP and PTP between the two groups, which suggested they would be involved in ERD. Then, logistic regression analysis was conducted to screen out the independent risk factors of ERD.

It was found that BP and PTP concentration were independent predictors of ERD occurrence.

The effective filtration pressure is associated with intra capillary pressure, tissue colloid osmotic pressure, plasma colloid osmotic pressure, and tissue hydraulic pressure. However the level of plasma osmotic pressure depends on the protein content in plasma, some studies have shown that the decrease of PTP or albumin content led to the decrease of plasma colloid osmotic pressure, it weakened the strength of tissue fluid flowing back to capillaries, then choroidal plasma leaked through RPE and its small closure zone which led to ERD[31-32], this was consistent with our results. In addition, we think that the increase of systolic BP lead to the rise of capillary internal pressure, which will promote the infiltration of tissue fluid into tissues, and cause damage of choroidal circulation, which will also lead to the occurrence of ERD.

ROC curve was used to analyze the diagnostic value of this algorithm: (maximum systolic pressure–plasma colloid osmotic pressure)/plasma colloid osmotic pressure. The AUC was as high as 0.933, and the cut-off value was 8.714 (Yoden index 0.778), with the corresponding sensitivity of 87.0% and specificity of 90.8%, respectively. Although it still needs a large number of samples to further verification, it seems feasible to predict and early sieve the high-risk PIH patients, its application may reduce stillbirth, small gestational age at delivery, lower birthweight, neonatal mortality, seizures, long-term coronary atherosclerotic heart disease and heart failure, which is great significant for early clinical intervention and improving the short-term and long-term prognosis of patients.

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