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A new predicting model of preeclampsia based on peripheral blood test values

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Abstract. – OBJECTIVE: To identify laboratory markers among platelet indices, coagulation parameters, blood lipid parameters, and liver/kidney function variables that can be used to predict preeclampsia.

PATIENTS AND METHODS: We studied records of 568 women with preeclampsia, gestational hypertension (GH), or normal term pregnancies hospitalized in the Obstetrics Department of the Fujian Maternal and Child Health Hospital from September 2014 to September 2018. We divided the patients' records into three groups (216 with preeclampsia, 136 with gestational hypertension, and 216 with normal pregnancies). We conducted retrospective analyses to compare variable measurements between the groups and find correlations. We looked into maternal pre-onset platelet indices, coagulation parameters (thrombin time [TT], fibrinogen [FIB]), biochemical parameters (total cholesterol [TC], triglycerides [TG], high-density lipoproteins [HDL], alanine transaminase [ALT], serum creatinine [CRE], blood urea nitrogen [BUN], uric acid [UA]), maternal complications, and perinatal outcomes. In addition to our statistical analysis, we trained a back-propagation (BP) neural network to identify the strongest predictors of preeclampsia.

RESULTS: We found significant differences among the groups in terms of values for PLT, MPV, PDW, PLCR, TT, FIB, TG, LDH, BUN, and others. After adjusting for confounding factors in a multivariate ordered logistic regression model, we found that mean values for MPV, BUN, TG, and LDH can independently predict the risk of preeclampsia (the OR values were 1.858, 1.583, 1.104, and 1.020, respectively), the C-index (concordance statistic) was 0.73. Also, our BP neural network derived ALB, MPV, BUN, LDH and TG as the strongest predictors of preeclampsia.

CONCLUSIONS: MPV, TG, LDH, and BUN can help establish the risk for the development of preeclampsia to apply active measures and improve maternal and perinatal outcomes. The BP neural network can be used to study predictive models of preeclampsia.

Key Words:
Preeclampsia, Platelet indices, Blood lipids, Liver and renal function tests.

Introduction

Hypertensive disorders during pregnancy (HDP) affect about 10% of pregnancies globally[1]. Preeclampsia occurs in 3-5% of all pregnancies, and is the leading cause of maternal and fetal perinatal morbidity and mortality[2]. Preeclampsia has a variety of clinical manifestations, and complicated pathological mechanisms involving multiple systems and organs. As a result, preeclampsia can lead to adverse pregnancy outcomes that include neurological sequelae for the neonate[3]. The etiology and pathogenesis of preeclampsia remain unclear. But, being able to predict the risk of preeclampsia before pregnancy is important to prevent complications or improve outcomes. The current screening methods are not effective, simple, and economic to be promoted and applied in areas with scarce medical resources. Thus, in this study, we compared different peripheral blood variables among groups of women with or without preeclampsia to find predictive indicators with high sensitivity and specificity to provide a basis for developing an economic and efficient screening program for preeclampsia.

Patients and Methods

Data Collection

To assess the predictive values of peripheral blood parameters for preeclampsia, we performed a retrospective case-control study with records of

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pregnant women at the Fujian Maternal and Child Health Hospital. The Local Ethics Committee approved the study (approval number 2018-088). We selected consecutive records of 568 women with preeclampsia, gestational hypertension, or normal full-term pregnancies at the Obstetrics Department dating from September 2014 to September 2018 (216 with preeclampsia, 136 with gestational hypertension, and 216 with normal full-term pregnancies).

The diagnostic criteria for gestational hypertension and preeclampsia were based on those published in Williams Obstetrics[4]. Preeclampsia: hypertension and plus one of below symptom: proteinuria (≥300 ug/24h or dipstick 1+ persistent), thrombocytopenia (platelet count<100,000/uL), renal insufficiency(creatinine level>1.1 mg/dl or doubling of baseline), liver involvement (serum transaminase levs twice normal), cerebral symptoms (headache, visual disturbance, convulsion), pulmonary edema. We excluded records of women with the following pre-existing conditions: chronic kidney disease, thrombocytopenia, lupus nephritis, chronic hypertension, coagulopathy, type 1 or type 2 diabetes, or antiplatelet, anticoagulation, glucocorticoid, or any other drug use that may affect peripheral blood variables.

All patients were followed up for 42 days after delivery, blood pressure and peripheral blood variables were measured until the normal ranges were reached in accordance to the Hospital's routine practice.

Measurement Methods

Patients had undergone routine blood tests when hospitalized for indications such as childbirth, abnormal fetal heart monitoring, etc. All the blood tests were performed before the preeclampsia clinical diagnosis. An automatic hematology system XE-5000 (Sysmex Corporation, Japan) was used to measure peripheral blood variables.

Statistical Analysis

We collected data for this study in a Microsoft Excel 2010 spreadsheet, and analyzed and plotted them using the SPSS 25.0 (IBM, Armonk, NY, USA) and R 3.6.0 software. We applied one-way ANOVA to evaluate the normal distribution of the continuous variables and used the SNK method for paired comparisons. We applied the Kruskal-Wallis H test for data with non-normal distribution or with heterogeneous variance. We used ordered logistic regression (best subsets method) to screen for independent influential factors of preeclampsia, and then constructed a nomogram prediction model according to selected independent factors to provide visual proof of preeclampsia risks. Finally, we evaluated the adequacy of prediction based on the Harrell's Consistency Index (C-index). We considered p-values <0.05 to be statistically significant.

Application of Back-Propagation Neural Network

For this study, we generated a three-layer BP neural network using TensorFlow to study the relevant variables affecting preeclampsia. We selected 25 potential influencing factors including ALB, MPV, and BUN to conduct detailed analyses. We collected a total of 568 samples from an equal number of women, we divided the sample data into training and testing data sets by a ratio of 2 to 1. The training data set consisted of 379 cases (144 with preeclampsia, 91 with GH, and 144 with normal pregnancies); the testing data set had 189 cases (72 with preeclampsia, 45 with GH, and 72 with normal pregnancy). For the three-layer neural network model, we used 25 influencing factors as the input neuron nodes, and three sample types as the output nodes. After training the neural network model, the weight values W1 of the input layer neuron nodes were obtained, and the correlation of the influencing factors was determined according to the magnitude of the weights.

Results

Analysis of General Clinical Data and Variables of the Three Different Groups

Comparison of General Data in the three groups

We found no significant differences in terms of pregnancy age, gravidity, and parity among the three groups of pregnant women (p>0.05). The mean BMIs and the gestational weeks at delivery were significantly different among the groups (p<0.05). However, we found similarities in terms of the mean variables between the preeclampsia and the gestational hypertension groups (p>0.05; Table I).

Single Factor Analysis of variables in the three groups

We found statistically significant differences (p<0.05) through univariate analyses in terms of PLT, MPV, PDW, PLCR, TT, FIB, UA, ALT, AST, ALB, TG, LDH, BUN, and CRE between the three groups of pregnant women. We performed paired comparisons using SNK (Table II and Figure 1).

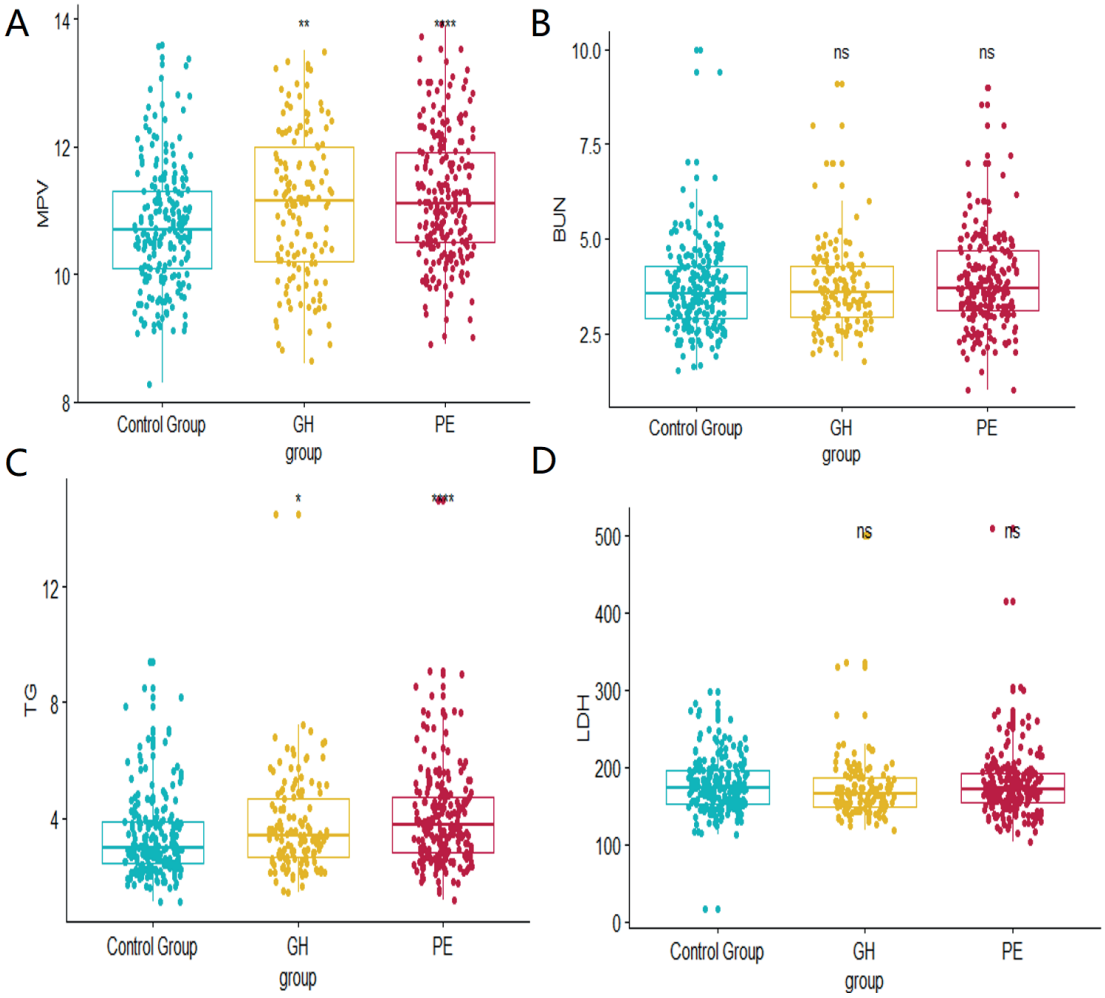

Figure 1. Independent sample Kruskall-Wallis test, Quantitative data showing **A**) MPV, **B**) TG, **C**) BUN, and **D**) LDH used for the control, the gestational hypertension (GH), and the preeclampsia groups. Box plot showing the data range (25-75%) and the data represent the means ± SDs.

Multivariate Logistic Regression Analysis with variables in the three groups

We first established an ordered logistic regression model utilizing all potential influential factors, and then applied the best subsets regression method to reduce the less viable predictors. We identified four preeclampsia predictive factors in the model: MPV (1.858), BUN (1.583), TG (1.104), and LDH (1.020) ordered by OR values (Table III).

Nomogram Model

To facilitate clinical evaluation and application, we used a logistic regression model and nomogram functions in R to plot the ordinal logistic

Table I. Comparison of general data of three groups of patients.

Group	Age (Kg/m²)	Admission BMI (times)	Gravidity (times)	Parity age	Gestational
Control group	30.99 ± 4.01	25.48 ± 3.70	1.90 ± 1.11	0.34 ± 0.51	39.55 ± 1.32
Pregnancy hypertension	30.13 ± 4.76	27.89 ± 5.08	2.04 ± 1.20	0.40 ± 0.59	38.89 ± 1.69
Preeclampsia	32.31 ± 21.20	27.60 ± 4.00	2.01 ± 1.26	0.42 ± 0.54	38.55 ± 2.09
p	0.310[a]	<0.001[a]	0.556[b]	0.281[b]	<0.001[b]

[a]ANOVA; [b]Kruskal-Wallis H test.

Table II. Single factor analysis of the test variables in the three groups of pregnant women.

Variables	Mean ± SD			*p*-value
	Control	Gestational hypertension	Preeclampsia	
PLT	211.73 ± 51.59	219.28 ± 61.01	202.31 ± 60.30[d]	0.022
MPV	10.74 ± 0.95	11.09 ± 1.16c	11.21 ± 1.01[c]	<0.001
PCT	0.47 ± 2.57	0.24 ± 0.06	0.22 ± 0.06	0.208
PDW	12.78 ± 2.33	13.65 ± 2.90c	13.81 ± 2.59[c]	<0.001
P-LCR	30.89 ± 7.65	33.37 ± 9.08c	34.39 ± 7.86[c]	<0.001
PT	11.07 ± 0.65	11.50 ± 1.22	11.48 ± 6.99	0.551
FDP	8.16 ± 4.82	7.06 ± 5.02	9.48 ± 21.68	0.269
TT	16.25 ± 0.86	16.09 ± 1.17	16.45 ± 1.40[d]	0.013
Fib	4.22 ± 0.63	4.37 ± 0.69	4.12 ± 0.87[d]	0.011
UA	310.38 ± 74.38	327.51 ± 80.79	358.41 ± 95.27[cd]	<0.001
ALT	12.24 ± 8.69	15.54 ± 8.07	20.27 ± 25.39[c,d]	<0.001
AST	16.27 ± 4.85	18.44 ± 7.18	21.74 ± 15.12[c,d]	<0.001
ALB	35.49 ± 2.02	34.30 ± 2.61	33.58 ± 3.47[c]	<0.001
TG	3.36 ± 1.36	3.97 ± 3.81	4.19 ± 3.82[c,d]	0.018
LDH	166.60 ± 29.98	164.39 ± 27.93	193.95 ± 59.12[c,d]	<0.001
BUN	3.43 ± 0.89	3.38 ± 0.56	4.18 ± 1.30[c,d]	<0.001
CRE	48.44 ± 9.05	51.26 ± 11.52	56.16 ± 12.34[c,d]	<0.001

[c]$p<0.05$ compared with the control group; [d]$p<0.05$ compared with the gestational hypertension group. PLT: platelet count; MPV: mean platelet volume; PCT: plateletocrit; PDW: platelet distribution width; P-LCR: platelet -larger cell ratio; PT: prothrombin time; FDP: fibrinogen degradation product; TT: thrombin time; Fib: fibrinogen; UA: uric acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: albumin; TG: triglyceride; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; CRE: creatinine.

Table III. Ordered logistic regression analysis of variables in the three groups to identify factors predictive of hypertensive disorders during pregnancy.

Co-variable	Regression coefficient	Standard error	*p*-value	Odds ration	95% CI of OR	
					Low limit	Upper limit
Intercept 1	-21.633	23.125	0.351	-	-	-
Intercept 2	-20.149	23.123	0.384	-	-	-
MPV	0.619	0.302	0.040	1.858	1.028	3.359
BUN	0.459	0.119	<0.001	1.583	1.253	2.000
TG	0.099	0.005	0.027	1.104	1.011	1.206
LDH	0.020	0.035	<0.001	1.020	1.013	1.027

regression nomograms (Figure 2). The nomogram provides a practical way to identify the risk of a pregnant woman to develop hypertensive disorders during pregnancy. We evaluated the model using Harrell's Consistency Index (C-index). The C index was 0.73 (indicating a medium predictive accuracy for the model).

Training Outcomes of BP Neural Network

We used 25 influential factors as the input neuron nodes for the neural network, and used 3 sample groups as the output nodes. The number of optimal hidden layer nodes was 10 after the experimental selection. Figure 3 shows the neural network structure.

From the structure of the neural network, W1 is a matrix with 25 rows and 10 columns, and the sum of the absolute values of the weights of each column is considered the weight of the corresponding influential factor of the column; when arranged in descending order, the BP neural network can derive the more predictive factors of preeclampsia among the input influential factors (the first 5 items; Table IV).

Table IV. Strongest predictors of preeclampsia among the influential factors derived by the BP neural network.

Factor	Metrics
ALB	3.6770
MPV	2.0633
BUN	1.6586
LDH	1.5478
TG	1.5028

We tested the predictive accuracy of the trained neural network using the testing sample set, and the results shown that the neural network was 79.8% correct. At the same time, from the data on Table IV can be seen that among the 25 factors studied, the top 5 factors with the greatest influence on preeclampsia are ALB, MPV, BUN, LDH and TG. We found similar results when using ordered logistic regression.

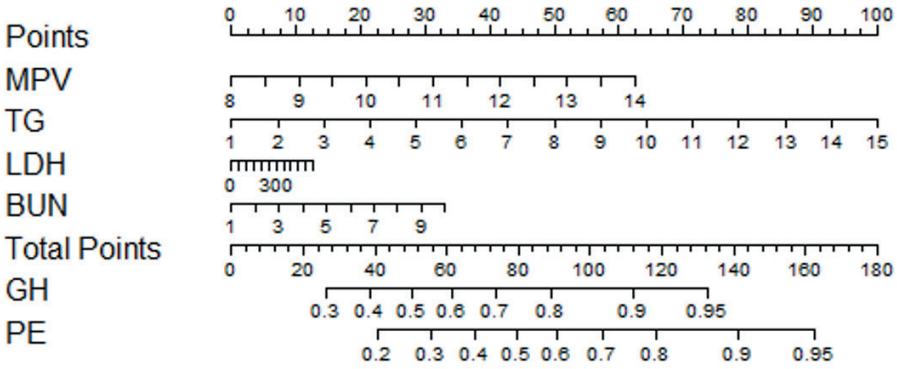

Figure 2. Nomogram of the preeclampsia prediction model.

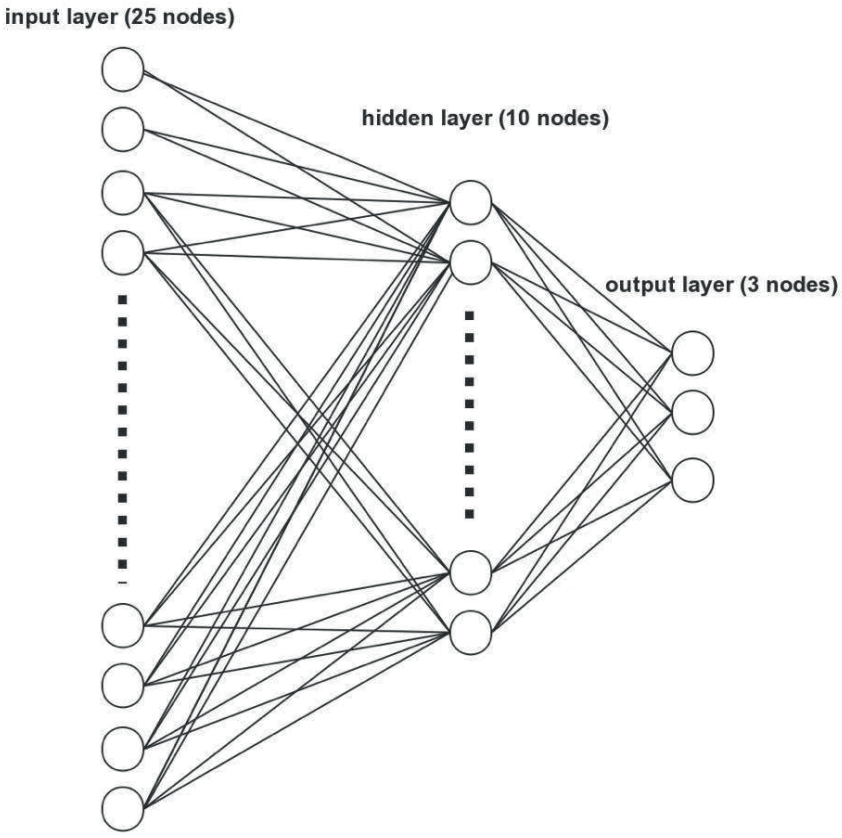

Figure 3. BP neural network structure.

Discussion

Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality. Prediction and screening preeclampsia for early detection, intervention, and treatment is important to improve maternal and infant outcomes. The current preeclampsia prediction method is difficult to promote and apply in areas with scarce medical resources. We retrospectively compared multiple laboratory variables in women with and without gestational hypertensive disorders to identify factors predicting development of preeclampsia using statistical analyses and a BP neural network. This prediction can guide early interventions before progress to overt preeclampsia to improve pregnancy outcomes.

Correlation Between Platelet Indices and Preeclampsia

Clinical platelet indices including PLT, MPV, plateletcrit (PCT), PDW, and PLCR are important variables for evaluating hemostasis and coagulation. The MPV can be used as an indirect indicator of bone marrow function. The average volume of platelets in growing or maturing stages is larger than that during aging stages, and an increase in the MPV reflects an enhancement of platelet activity. In addition, an elevated MPV may be associated with impaired uterine placental circulatory function[5]. When exposed to damaged vascular endothelial cells, platelets in patients with preeclampsia get activated for coagulation, and the platelet consumption is increased. Depleted platelet counts trigger the bone marrow to produce new platelets, thereby increasing the MPV. Additionally, newly formed platelets are also more active than mature and aging ones in terms of their metabolism and functionality. Majed and Khalil[6] showed that women who eventually developed preeclampsia had signs of platelet activation during early pregnancy. This may be due to the trophoblasts cells invading the spiral artery in the uterus placenta and activating new platelet formation[7]. The maternal MPV values in women with preeclampsia were significantly higher than those of patients with normal blood (from the 24th week of gestation to the end of delivery), and the diagnostic sensitivity of MPV for preeclampsia was significantly higher than that of PLT[8]. Our results showed that the MPV levels in the preeclampsia and gestational hypertensive groups were higher than those in the normal group, and the differences were statistically significant. Moreover, a high MPV level was an independent risk factor for preeclampsia. Our results also suggested that in the preeclampsia and gestational hypertensive groups, the formation of platelets was more active. This suggests that platelet function variables should be tested throughout pregnancy, and that women with signs of activated platelet formation during early pregnancy have a high risk of developing preeclampsia.

Correlation Between Blood Lipid Levels and Preeclampsia

The TGs in adipose tissue are the main form of energy storage in the body. Levels of TC, TG, and low-density lipoprotein (LDL) are elevated in the blood of pregnant women[9]. These changes are considered to be adaptive adjustments to support fetal development. Studies[10,11] have shown that dyslipidemia does not only increase cardiovascular disease risk, but it also causes adverse pregnancy outcomes and induces preeclampsia. Studies[11-13] that levels of blood TC and TG are higher in women with preeclampsia than those in pregnant women without it. Our results showed that the mean TG level in the preeclampsia group was significantly higher than those in the normal and hypertensive groups. In addition, the elevated TG level was an independent risk factor for preeclampsia. We found the differences in blood lipid TC and LDL were not statistically significant between the groups, similar to reported results[11,13].

Correlation Between the Liver Function Variables and Preeclampsia

The main energy supply pathway to the placenta occurs through glycolysis. LDH is an intracellular enzyme required for glycolysis. Under hypoxic conditions, LDH is activated to promote glycolysis and produce large amounts of lactic acid. As a result, elevated levels of LDH often suggest cell damage and dysfunction. Elevated levels of LDH in patients with preeclampsia have been associated with adverse pregnancy outcomes for mother and child[14,15]. Our results showed that the LDH levels of patients with preeclampsia were significantly higher than those of the normal and the hypertensive groups during the third trimester of pregnancy, suggesting a correlation between LDH and the severity of the disease.

ALB is an important indicator of the liver's synthetic function and maintains the blood colloid osmotic pressure. Vascular endothelial cells are damaged in patients with preeclampsia and severe complications, and the action of angio-

tensin increases vascular permeability leading to the loss of plasma proteins (especially ALB) and a decrease in plasma colloid osmotic pressure that accelerates the appearance of intravascular lesions. Dai et al[16] found that the levels of ALB in patients with gestational hypertension or chronic hypertension were lower than those in normal pregnant women. In this study, we found that the levels of albumin in the preeclampsia group were significantly lower than those in the normal group. The BP neural network model also showed that the ALB levels affect preeclampsia, although the multivariate regression model showed that ALB was not an independent risk for preeclampsia. The different results from our two approaches need to be verified by a larger study in the future. In all, liver function tests can be used to assess the severity of preeclampsia, LDH elevation and ALB reduction are often associated with adverse pregnancy outcomes.

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Correlation Between Renal Function Variables and Preeclampsia

Patients with preeclampsia are prone to organ and tissue ischemia and hypoxia damage. The kidneys are especially sensitive to this type of damage and an acute kidney injury in a woman with PR may persist after delivery[17]. Abnormal renal function's variables can provide a marker for the early detection of patients with preeclampsia, who undergo small renal artery spasms that trigger glomerular swelling, glomerular filtration rate, and renal blood flow reductions, which can lead to renal excretion dysfunction and the resulting blockage of excretion and removal of renal metabolites such as BUN, UA, and CRE[18].

Urea nitrogen is the main end product of human protein metabolism. The concentration of BUN depends on the catabolism of proteins, the amount of protein in food, and the ability of the kidney to excrete. When food intake and catabolism in the body are relatively stable, the concentration depends on the ability of the kidney to excrete. Due to the strong reserve capacity of the glomeruli, serum BUN indicators do not change significantly unless the renal function is severely impaired. The normal range of clinical serum BUN is 2.5-6.5 mmol / L; when BUN is higher than that, 60-70% of the effective nephrons have been damaged. Our results showed that the levels of urea nitrogen in the preeclampsia group were significantly higher than those in the normal and the hypertensive groups, and an elevated level of urea nitrogen was an independent risk factor for preeclampsia.

Conclusions

Monitoring MPV, BUN, TG, and LDH levels during routine examinations can help predict the development of preeclampsia, and provide guidance in medical institutions with inadequate medical resources. By analyzing the associations between peripheral blood variables and preeclampsia, we were able to establish a simple, economic, fast, and effective prediction model that helps to close the gap for preeclampsia prediction. Our research found that the use of routine examinations to predict PE has a certain effect, and for the first time, the results of neural network analysis prompted the evaluation of the weights of different indicators, which played an intuitive role in the preliminary assessment of the condition of primary doctors.

This prediction can guide early interventions before progress to overt preeclampsia to improve pregnancy outcomes.

Author Contributions

QH, WZ and JY conceived and designed the study, XG, DZ and HL collected data and performed data analysis. QH and WZ wrote the draft of this manuscript. LY, JY and QH edited the manuscript.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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