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Risk Prediction Model for Hypertensive Disorders of Pregnancy Based on Routine Laboratory Indicators and Risk Factors: A Retrospective Analysis

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Abstract

Background: Hypertensive disorder of pregnancy (HDP) is a group of diseases in which pregnancy and elevated blood pressure coexist. There is still a lack of reliable clinical tools to predict the incidence of HDP. The purpose of this study was to establish and validate a nomogram prediction model for assessing the risk of HDP in pregnant women based on laboratory indicators and HDP risk factors. **Method:** A total of 307 pregnant women who were hospitalized in the obstetrics and gynecology department of our hospital were included in this study, and were randomly divided into a training cohort and validation cohort at a ratio of 7:3. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for the development of HDP on laboratory indicators as well as risk factors for HDP in the training cohort of patients. The results of the multivariate regression model were visualized by forest plots. A nomogram was constructed based on the results of multivariate logistic regression to predict the risk of HDP in pregnant women. The validity of the risk prediction model was evaluated by the area under the receiver operating characteristic curve (AUC), the consistency index (C-index), the calibration curve and the decision curve analysis (DCA). **Results:** BMI ≥ 25 Kg/m^2, total cholesterol in early pregnancy, uric acid and proteinuria in late pregnancy were independent risk factors for HDP. The AUC and C-index of the nomogram constructed by the above four factors were both 0.848. The calibration curve is closely fitted with the ideal diagonal, showing a good consistency between the nomogram prediction and the actual observation of HDP. The DCA has demonstrated the great clinical utility of nomogram. Internal verification proves the reliability of the predicted nomograms.

Conclusion: The BTUP nomogram model based on laboratory indicators and risk factors proposed in this study showed good predictive value for the risk assessment of HDP. It is expected to provide evidence for clinical prediction of the risk of HDP in pregnant women.

Keywords

Hypertensive Disorders of Pregnancy, Nomogram, Laboratory Indicators, Risk Factors

1. Background

Hypertensive disorder of pregnancy (HDP) is a group of diseases with pregnancy and elevated blood pressure, which is often characterized by systemic, progressive and multiple organ involvement. The 5 categories of HDP are gestational hypertension, preeclampsia, eclampsia, chronic hypertension with pregnancy and chronic hypertension with preeclampsia. Severe pregnancy-induced hypertension such as severe preeclampsia may lead to adverse outcomes like maternal and infant death. Hypertensive disorder of pregnancy (HDP) remains one of the most important public health problems [1]. More than 200,000 stillbirths are attributable to pre-eclampsia and eclampsia, with two regions, sub-Saharan Africa and South Asia, carrying the highest burden [2]. One of the reasons for the high mortality rate of pregnant women caused by HDP is the lack of reliable means to early identify high-risk pregnant women who may have HDP [3].

Now there are many clinical studies that incorporate different variables to construct models to predict the risk of developing HDP disease [4]-[7]. However, a large number of published studies have failed to reach a consensus on the best strategy. Most of them predicted the risk of preeclampsia rather than HDP, and lacked sufficient performance testing [5] [8]. A nomogram is a tool widely used to evaluate the prognosis of patients. One of its advantages is that it can assess the individual risk of patients by integrating multiple prognoses and decisions based on individual disease characteristics [9] [10].

2. Materials and Methods

2.1. Type, Location, Period and Duration of the Study

This was an observational study with retrospective data collection carried out in the obstetrics and gynecology department of Beijing Tongren Hospital from January 2022 to January 2024, i.e. a duration of 2 years.

2.2. Study Population and Design

A total of 187 pregnant women who were hospitalized in the Department of Obstetrics and Gynecology, Beijing Tongren Hospital, Capital Medical University from January 2022 to February 2024 were included in the study as the Hypertensive

disorder of pregnancy group (HDP group). Another 120 pregnant women who were hospitalized in our hospital and delivered normally during the same period were selected as the control group (CON group). Finally, 307 pregnant women were included in the study and randomly divided into a training cohort and a validation cohort at a ratio of 7:3.

2.3. Criteria

2.3.1. Inclusion Criteria

HDP group: 1) Pregnant women who were admitted to our hospital between January 2022 and January 2024 and met the diagnostic criteria for "Diagnosis and treatment of hypertension and pre-eclampsia in pregnancy: a clinical practice guideline in China (2022)" [11]. 2) The patients were cooperative and had no psychiatric disorders of consciousness to ensure the credibility of the data.

CON gourp: Healthy pregnant women who were admitted to our hospital between January 2022 and January 2024 who did not qualify for a diagnosis of gestational hypertension and had a normal delivery.

2.3.2. Exclusion and Non-Inclusion Criteria

1) Patients who did not meet inclusion criteria.

2) Presence of patients with significant missing information.

2.4. Ethics

This study is a retrospective study. Subjects' privacy and personally identifiable information were protected, and therefore informed consent was approved to be waived.

2.5. Data and Sample Collection

The general data of patients were obtained from electronic cases, including age of admission, gestational age, pregnancy history, medical history, and pre-pregnancy BMI. A total of 6 risk factors for hypertensive disorders in pregnancy, including pre-pregnancy BMI ≥ 25 Kg/m^2, age ≥ 35 years, primiparity, gestational diabetes mellitus (GDM), polycystic ovary syndrome, thyroid disease, etc.; Routine laboratory indicators: including uric acid, proteinuria, alanine (ALT), aspartate (AST), blood calcium, lactate dehydrogenase (LDH), triglyceride (TG), total cholesterol (TC), lipoprotein (a) [LP(a)], platelet (Plt), hemoglobin (Hb), fibrinogen (Fib), D-dimer (D-D), high-sensitivity C-reactive protein, a total of 14 indicators. The human data were performed in accordance with the Declaration of Helsinki. This study is a retrospective observational study, which is conducted using only case data and does not adversely affect the rights and health of the subjects, and is therefore exempt from ethical review.

2.6. Statistical Analysis

SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The GraphPad Prism 8 software is used to create visual forest maps. Count

data were expressed as the number of cases (percentage), and the chi-square test was used for comparison between cohorts. Normal distribution data were expressed as mean ± standard deviation, and the comparison between the two cohorts was performed by independent sample t-test. Non-normal distribution was expressed as median (interquartile range), and the Mann-Whitney U test was used for comparison between the two cohorts.

Univariate and multivariate binary logistic regression analysis was used to evaluate the correlation between various risk factors as well as laboratory indicators and the incidence of HDP in the training cohort, and the results of the multivariate regression model were visualized by forest plots. According to the results of multivariate logistic regression analysis, a nomogram was established to predict the risk of HPD. The area under the receiver operating characteristic curve (AUC) and the consistency index (C-index) were used to evaluate the prediction accuracy. Calibration plots were used to further evaluate the consistency of the nomogram. The actual clinical application performance of the nomogram was evaluated by decision curve analysis (DCA). The prediction performance of the nomogram is verified by the validation cohort.

3. Results

3.1. Patient Information

A total of 307 eligible patients were enrolled, 214 of which were included in the training cohort, while 93 were included in the validation cohort. Table 1 summarizes the characteristics of the study population. There was no significant difference between the two cohorts in general characteristics (age, gestational weeks, pre-pregnancy BMI, gestational weight gain), risk factors (GDM, PCOS, thyroid disease, pre-pregnancy BMI ≥ 25Kg/m^2, age ≥ 35 years, primipara), laboratory indicators (FIB, D-D, uric acid, early pregnancy urinary protein, ALT, AST, LDH, TG, TC, Lp(a), Hb, Plt, high-sensitivity CRP, blood calcium) (P > 0.05).

Table 1. Comparison between training cohort and validation cohort.

Factor	Training cohort (n = 214)	Validation cohort (n = 93)	P
General Characteristics			
Age (years)	32.00 (29.00, 35.00)	31.00 (29.00, 35.00)	0.313
Gestational weeks (weeks)	38.00 (37.0, 39.00)	38.00 (37.00, 39.00)	0.674
Pre-pregnancy BMI (kg/m^2)	22.72 (21.61, 24.60)	23.23 (21.65, 25.61)	0.610
Gestational weight gain (Kg)	13.00 (10.00, 17.00)	13.00 (10.00, 15.00)	0.169
Risk Factors [n/(%)]			
GDM	40 (30.3)	19 (34.5)	0.281
PCOS	13 (9.8)	1 (1.8)	0.859
Thyroid disease	21 (15.9)	12 (21.8)	0.324
Pre-pregnancy BMI ≥ 25 kg/m^2	36 (27.3)	16 (29.1)	0.186

Continued

Age ≥ 35	38 (28.8)	12 (21.8)	0.814
Primiparity	100 (75.8)	45 (81.8)	0.888
Early Pregnancy Laboratory Indicators			
Fib(g/L)	3.38 (3.06, 3.71)	3.48 (3.02, 3.86)	0.589
D-D (mg/L)	0.32 (0.23, 0.45)	0.31 (0.20, 0.45)	0.167
Uric acid (μmol/L)	236.50 (195.00, 266.25)	236.50 (195.50, 271.50)	0.641
Proteinuria [n/(%)]	59 (27.6)	21 (22.6)	0.360
ALT (U/L)	13.00 (11.00, 18.00)	14.00 (11.50, 20.00)	0.063
AST (U/L)	16.00 (14.00, 18.00)	17.00 (15.00, 19.00)	0.296
LDH (U/L)	144.50 (131.00, 155.00)	143.00 (131.50, 161.00)	0.713
TG (mmol/L)	0.99 (0.78, 1.23)	0.97 (0.76, 1.29)	0.915
TC (mmol/L)	4.17 ± 0.68	4.12 ± 0.58	0.533
Lp(a) (mg/μL)	9.40 (4.50, 16.73)	9.85 (5.35, 18.50)	0.388
Hb (g/L)	129.00 (123.00, 135.00)	131.00 (125.00, 137.00)	0.129
Plt (10^9/L)	254.50 (220.00, 280.00)	264.00 (226.00, 303.00)	0.099
High sensitive CRP (mg/L)	1.20 (0.68, 2.7)	1.20 (0.70, 2.75)	0.997
Ca (mmol/L)	2.34 ± 0.08	2.35 ± 0.08	0.656
Late Pregnancy Laboratory Indicators			
Fib (g/L)	4.50 ± 0.73	4.58 ± 0.73	0.330
D-D (mg/L)	1.66 (1.17, 2.15)	1.66 (1.32, 2.08)	0.559
Uric acid (μmol/L)	323.50 (281.00, 391.50)	313.00 (257.50, 369.00)	0.159
Proteinuria [n/(%)]	87 (40.7)	23 (24.7)	0.008
ALT (U/L)	10.00 (8.00, 13.00)	10.00 (8.00, 14.00)	0.859
AST (U/L)	17.00 (15.00, 19.00)	16.00 (14.00, 18.00)	0.175
LDH (U/L)	165.00 (148.00, 182.00)	163.00 (143.50, 174.50)	0.147
TG (mmol/L)	3.45 (2.78, 4.09)	3.28 (2.72, 4.16)	0.872
TC (mmol/L)	6.21 (5.61, 6.89)	6.41 (5.93, 7.08)	0.061
Lp(a) (mg/μL)	10.9 (5.25, 19.83)	12.30 (5.80, 22.70)	0.185
Hb (g/L)	122.00 (115.50, 129.00)	122.00 (115.00, 126.50)	0.637
Plt (10^9/L)	190.00 (160.00, 220.25)	199.00 (169.50, 224.00)	0.109
High sensitive CRP (mg/L)	4.03 (2.28, 6.80)	4.05 (2.20, 6.15)	0.894
Ca (mmol/L)	2.22 (2.15, 2.28)	2.24 (2.15, 2.30)	0.083

*P-value < 0.05.

Table 2 compares the characteristics between the CON group and the HDP group in the two cohorts. In the training cohort, there were significant differences between the HDP group and the CON group in the general characteristics including gestational weeks and pre-pregnancy BMI (continuous value), risk factors including GDM, PCOS, pre-pregnancy BMI ≥ 25 kg/m^2, Primiparity, laboratory

indicators including TG, TC, Hb, Plt, serum calcium in the first trimester, uric acid, proteinuria, LDH, TG in the third trimester ($P < 0.05$). In the validation cohort, there were significant differences between the HDP group and the CON group in risk factors such as thyroid disease and primiparity, laboratory indicators such as Plt and serum calcium in the first trimester, and uric acid, proteinuria, LDH and TG in the third trimester ($P < 0.05$).

Table 2. Comparison between CON group and HDP group in two cohorts.

Factor	Training cohort (n = 214)			Validation cohort (n = 93)		
	HDP group (n = 132)	CON group (n = 82)	P	HDP group (n = 55)	CON group (n = 38)	P
General Characteristics						
Age (years)	32.00 (29.00, 35.00)	32.00 (30.00, 34.25)	0.99	31.00 (29.00, 34.00)	31.50 (28.00, 35.25)	0.78
Gestational weeks (weeks)	38.00 (37.0，39.00)	38.00 (38.00, 39.00)	0.00*	38.00 (37.00, 39.00)	38.00 (37.00, 39.00)	0.96
Pre-pregnancy BMI (kg/m^2)	23.36 (21.77, 25.13)	22.30 (21.29, 23.03)	0.00*	23.36 (21.77, 25.70)	22.30 (20.95, 25.56)	0.20
Gestational weight gain (Kg)	13.76 (10.00, 17.88)	13.00 (10.75, 15.25)	0.47	12.76 ± 3.75	12.82 ± 5.49	0.95
Risk Factors [n/(%)]						
GDM	40 (30.3)	14 (17.1)	0.03*	19 (34.5)	10 (26.3)	0.40
PCOS	13 (9.8)	2 (2.4)	0.04*	1 (1.8)	4 (10.8)	0.16
Thyroid disease	21 (15.9)	17 (20.7)	0.40	12 (21.8)	29 (76.3)	<0.0*
Pre-pregnancy BMI ≥ 25 kg/m^2	36 (27.3)	9 (11.0)	0.00*	16 (29.1)	10 (26.3)	0.77
Age≥35	38 (28.8)	20 (24.4)	0.48	12 (21.8)	12 (31.6)	0.29
Primiparity	100 (75.8)	49 (59.8)	0.01*	45 (81.8)	19 (50.0)	0.00*
Early Pregnancy Laboratory Indicators						
Fib(g/L)	3.41 (3.03, 3.76)	3.36 (3.08, 3.70)	0.98	3.50 ± 0.57	3.38 ± 0.52	0.27
D-D (mg/L)	0.32 (0.22, 0.50)	0.31 (0.24, 0.44)	0.47	0.31 (0.20, 0.52)	0.29 (0.22, 0.37)	0.53
Uric acid (μmol/L)	239.02 ± 53.67	231.59 ± 48.92	0.34	234.01 ± 54.06	246.72 ± 51.65	0.26
Proteinuria [n/(%)]	41 (31.1)	18 (22.0)	0.15	13 (23.6)	8 (21.2)	0.77
ALT (U/L)	14.00 (11.00, 19.00)	13.00 (10.75, 15.25)	0.70	14.00 (12.00, 20.00)	13.00 (10.75, 19.25)	0.29
AST (U/L)	16.00 (14.00, 18.00)	16.00 (15.00, 19.00)	0.74	17.00 (15.00, 19.00)	16.00 (14.00, 20.00)	0.51
LDH (U/L)	144.50 (138.00, 155.00)	145.00 (129.00, 153.00)	0.28	140.00 (129.00, 161.00)	147.00 (133.75, 164.75)	0.13
TG (mmol/L)	1.03 (0.84, 1.32)	0.89 (0.73, 1.11)	<0.00*	1.00 (0.77, 1.35)	0.89 (0.72, 1.23)	0.27
TC (mmol/L)	4.34 ± 0.68	3.91 ± 0.59	<0.00*	4.18 ± 0.61	4.04 ± 0.52	0.24
Lp(a) (mg/μL)	9.85 (5, 21.125)	9.30 (4.4, 14.53)	0.26	9.85 (7.60, 21.80)	9.3 (4.90, 14.23)	0.07
Hb (g/L)	130.00 (124.00, 136.00)	128.00 (123.00, 132.00)	0.01*	131.00 ± 8.35	130.55 ± 6.95	0.79
Plt(10^9/L)	266.00 (234.75, 283.75)	235.00 (209.75, 270.00)	<0.00*	273.76 ± 46.79	247.61 ± 54.05	0.02*
High sensitive CRP (mg/L)	1.20 (0.60, 3.00)	1.20 (0.70, 2.13)	0.52	1.20 (0.80, 2.80)	1.30 (0.48, 2.43)	0.46

Continued

Ca (mmol/L)	2.36 ± 0.08	2.33 ± 0.07	0.00*	2.37 ± 0.08	2.33 ± 0.07	0.02*
Late Pregnancy Laboratory Indicators						
Fib(g/L)	4.47 ± 0.79	4.54 ± 0.64	0.46	4.49 ± 0.78	4.71 ± 0.65	0.16
D-D (mg/L)	1.66 (1.14, 2.19)	1.68 (1.27, 2.05)	0.93	1.66 (1.31, 2.14)	1.70 (1.33, 2.07)	0.84
Uric acid (μmol/L)	370.21 ± 87.34	285.96 ± 57.49	<0.00*	362.62 ± 86.08	267.63 ± 49.06	<0.00*
Proteinuria [n/(%)]	67 (50.8)	20 (24.4)	<0.00*	18 (32.7)	5 (13.2)	0.03*
ALT (U/L)	10.00 (8.00, 13.00)	10.00 (8.75, 13.00)	0.91	10.00 (8.00, 13.00)	10.00 (8.75, 14.25)	0.55
AST (U/L)	17.00 (15.00, 20.75)	16.00 (15.00, 18.00)	0.08	16.78 ± 3.24	15.92 ± 3.39	0.22
LDH (U/L)	166.00 (149.50, 192.50)	158.50 (145.00, 174.50)	0.01*	16.78 ± 3.24	154.51 ± 23.75	0.04*
TG (mmol/L)	3.59 (2.88, 4.36)	3.02 (2.56, 3.70)	0.00*	3.64 (3.11, 4.73)	3.00 (2.37, 3.61)	<0.00*
TC (mmol/L)	6.21 (5.69, 6.73)	6.41 (5.56, 7.11)	0.26	6.21 (5.85, 7.04)	6.43 (6.15, 7.19)	0.22
Lp(a) (mg/μL)	10.40 (5.00, 19.38)	12.30 (6.13, 21.85)	0.12	11.00 (6.20, 25.80)	12.30 (5.55, 21.95)	0.95
Hb (g/L)	194.36 ± 49.21	191.29 ± 39.50	0.85	121.36 ± 9.33	120.95 ± 9.90	0.84
Plt(10^9/L)	194.02 ± 52.87	194.02 ± 52.87	0.62	204.00 (174.00, 237.00)	186.00 (166.25, 220.00)	0.08
High sensitive CRP (mg/L)	4.05 (2.43, 7.60)	3.38 (1.95, 5.80)	0.04	4.05 (2.20, 8.30)	3.70 (1.90, 5.78)	0.30
Ca (mmol/L)	2.21 ± 0.12	2.21 ± 0.07	0.87	2.25 ± 0.12	2.22 ± 0.08	0.27

*P-value < 0.05.

3.2. Nomogram Development

Univariate logistic regression analysis and multifactor logistic regression analysis were carried out in this study in sequence. Univariate logistic analysis showed that a total of 14 factors including risk factors of GDM, pre-pregnancy BMI, primiparity, laboratory indicators of TG, TC, Hb, Plt, serum calcium in the first trimester, uric acid, proteinuria, AST, LDH, TG, high-sensitivity CRP in the third trimester in late pregnancy were closely related to the occurrence of HDP (P < 0.05). Multivariate Logistic analysis was performed on these 14 variables, and finally 4 variables with *P* values < 0.05 were obtained: pre-pregnancy BMI ≥ 25 Kg/m^2, TC in the first trimester, uric acid and proteinuria in the third trimester. Table 3 shows the detailed information of univariate and multivariate Logistic analysis results. Display the results of multivariate logistics regression through the forest map (Figure 1). The forest map showed that BMI ≥ 25 Kg/m^2, TC in early pregnancy, uric acid and proteinuria in late pregnancy were not intersected with the invalid line (all P < 0.05), and were all positive risk factors for HDP.

Table 3. Analysis of influencing factors of HDP in the training cohort.

Variables	Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P
Risk Factors [n/(%)]						
GDM						

Continued

Yes	2.104	1.060~4.175	0.03*	1.140	0.441~2.952	0.79
No	1			1		
PCOS						
Yes	4.370	0.960~19.888	0.06			
No	1					
Thyroid disease						
Yes	0.712	0.350~1.448	0.35			
No						
Pre-pregnancy BMI						
<25	1			1		
≥25	3.042	1.379~6.711	0.01*	3.231	1.170 ~8.919	0.02 *
Age						
<35	1					
≥35	1.253	0.668~2.351	0.48			
Primiparity						
Yes	2.105	1.162~3.813	0.01*	1.888	0.822 ~4.336	0.13
No	1			1		
Early Pregnancy Laboratory Indicators						
Fib(g/L)	1.021	0.607~1.717	0.94			
D-D (mg/L)	2.849	0.781~10.396	0.11			
Uric acid (μmol/L)	1.003	0.997~1.008	0.31			
Proteinuria [n/(%)]	1.602	0.845~3.037	0.15			
ALT (U/L)	1.036	0.987~1.089	0.16			
AST (U/L)	0.974	0.897~1.057	0.53			
LDH (U/L)	1.09	0.993~1.024	0.27			
TG (mmol/L)	4.569	1.895~11.016	0.00*	2.952	0.794~10.980	0.11
TC (mmol/L)	2.891	1.785~4.683	<0.00*	2.122	1.099~4.096	0.03*
Lp(a) (mg/μL)	1.019	0.996~1.043	0.10			
Hb (g/L)	1.038	1.006~1.071	0.02*	1.042	0.995~1.092	0.08
Plt(10^9/L)	1.011	1.005~1.018	<0.00*	0.999	0.990 ~1.008	0.82
High sensitive CRP(mg/L)	1.113	0.956~1.295	0.17			
Ca (mmol/L)	465.027	9.949~21736.081	0.00*	39.413	0.269~5772.358	0.15
Late Pregnancy Laboratory Indicators						
Fib(g/L)	0.867	0.594~1.266	0.46			
D-D (mg/L)	1.092	0.722~1.650	0.68			
Uric acid (μmol/L)	1.016	1.010~1.022	<0.00*	1.014	1.008~1.020	<0.00*

Continued

Proteinuria [n/(%)]	3.195	1.739~5.873	<0.00*	2.244	1.020 ~4.936	0.04*
ALT (U/L)	1.025	0.958~1.096	0.48			
AST (U/L)	1.078	1.004~1.158	0.04*	1.059	0.960~1.167	0.25
LDH (U/L)	1.012	1.002~1.021	0.01*	1.010	0.997~1.023	0.13
TG (mmol/L)	1.621	1.226~2.144	0.00*	1.111	0.768 ~1.606	0.58
TC (mmol/L)	0.879	0.671~1.152	0.35			
Lp(a) (mg/μL)	0.982	0.963~1.001	0.07			
Hb (g/L)	1.002	0.977~1.029	0.86			
Plt(10^9/L)	1.001	0.995~1.008	0.63			
High sensitive CRP(mg/L)	1.101	1.023~1.184	0.01*	1.050	0.965~1.143	0.26
Ca (mmol/L)	0.816	0.060~11.191	0.88			

*P-value < 0.05.

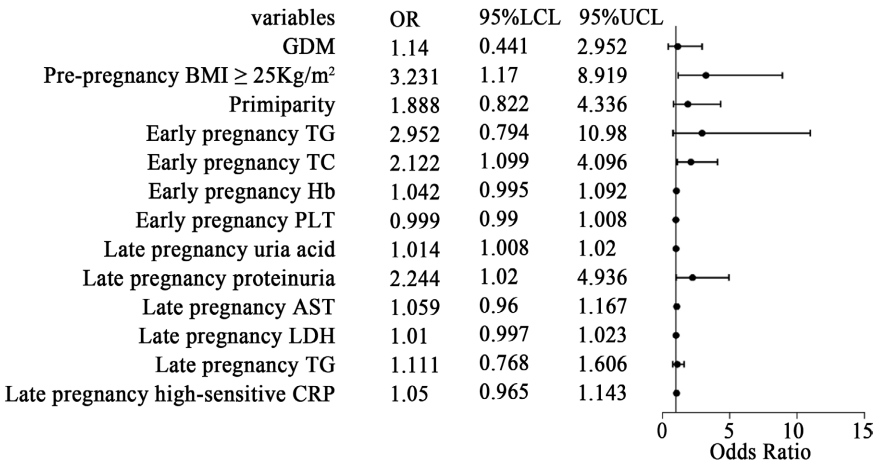

Figure 1. Forest map showing the results of multivariate logistic regression.

Based on the above four variables, a nomogram was constructed to predict the risk of gestational hypertension in pregnant women (**Figure 2**). For each pregnant woman, the higher the total score, the greater the risk of hypertension in life.

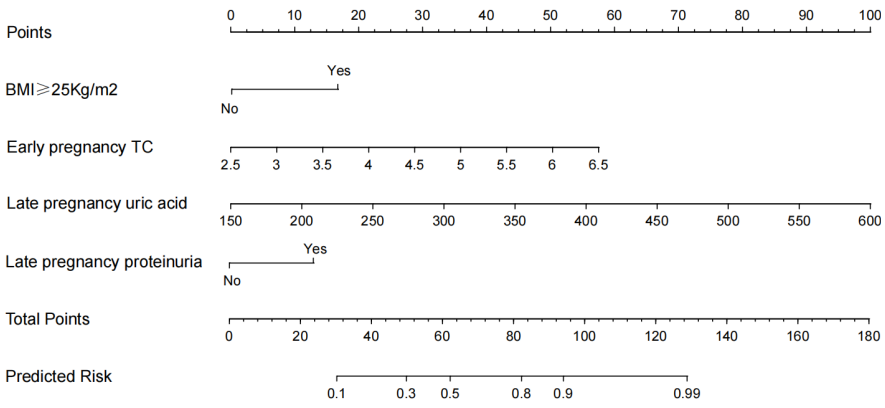

Figure 2. The nomogram for predicting HDP.

3.3. Nomogram Validation

The C index in the training cohort was 0.847 (95% CI, 0.796 - 0.900), which was consistent with the AUC value (Figure 3A). The calibration curve is closely fitted with the ideal diagonal (Figure 4A). In addition, DCA shows that the nomogram provides a favorable net benefit. (Figure 5A). In addition, 93 patients who were hospitalized in the obstetrics and gynecology department of our hospital during the same period were included as a validation cohort for internal validation to test the nomogram. The AUC value was 0.847 (Figure 3B), reflecting the good accuracy of the nomogram. The calibration curve of the Validation cohort is also close

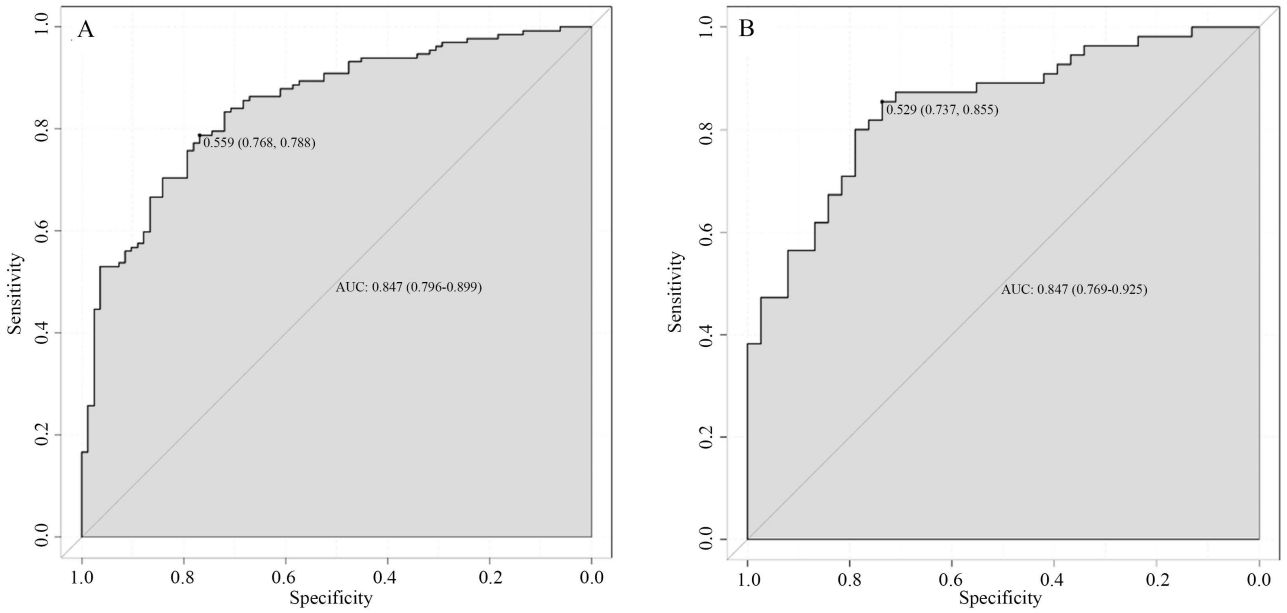

Figure 3. ROC curve. (A) Training cohort. (B) Validation cohort. ROC, receiver operating curve; AUC, area under the ROC curve.

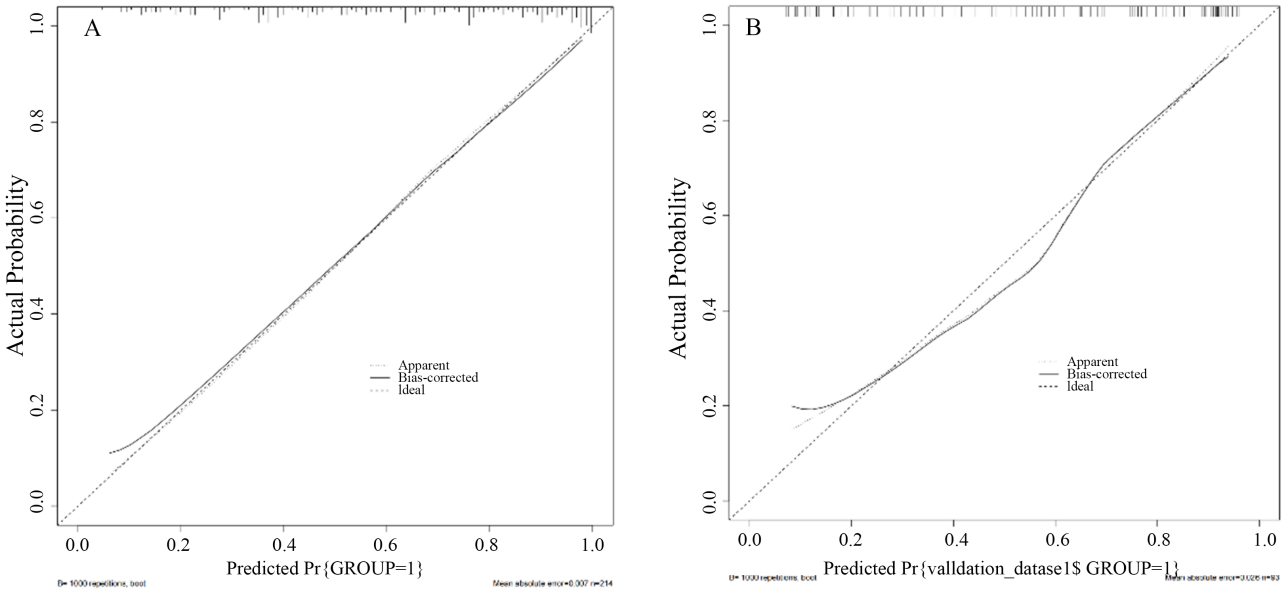

Figure 4. Calibration curve for the risk of HDP. (A) Training cohort. (B) Validation cohort.

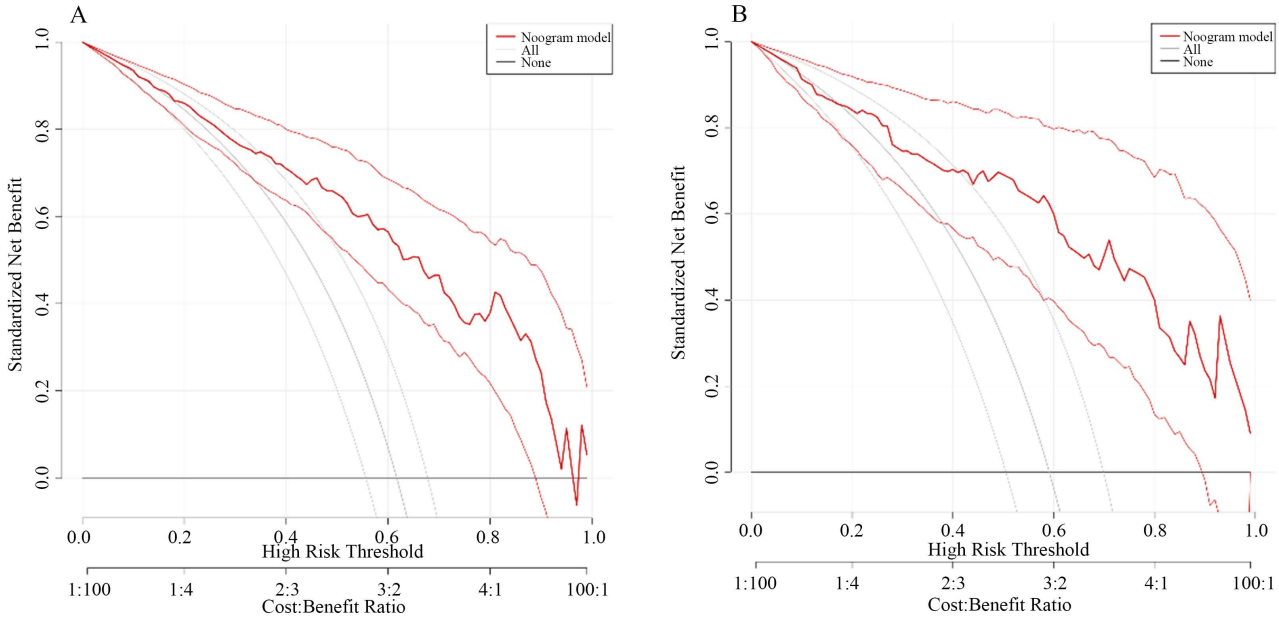

Figure 5. Decision curve analysis of the risk of HDP. (A) Training cohort. (B) Validation cohort.

to the ideal diagonal, showing a good consistency between the nomogram prediction and the actual event (**Figure 4B**). Moreover, DCA showed that the nomogram provided significant net benefits, suggesting that the nomogram had great clinical practicality (**Figure 5B**). These data suggest that our nomogram has great potential for clinical decision-making.

4. Discussion

HDP is not only associated with an increased risk of maternal and infant complications during and after pregnancy, pregnant women with a history of HDP are also at increased risk for future cardiovascular disease. Therefore, early identification of women at risk of HDP is important for the prevention of both current and future mortality and morbidity [12]. How to prevent the occurrence of HDP is still the most concerned issue for clinicians. Traditional risk prediction model research population mainly comes from high-income countries. The prediction results focus on eclampsia among HDP diseases, and the research indicators included vary. Lack of external, internal validation and model calibration reports are also common problems in traditional risk prediction models [6]. This present study included Chinese pregnant women hospitalized in our hospital as the research object. The common HDP risk factors and routine laboratory indicators of prenatal examination were used as risk predictors to establish a nomogram risk prediction model, and the calibration curve and DCA were used in internal verification to verify the consistency and clinical application efficiency of the nomogram. Besides, common HDP risk factors and routine laboratory indicators are included for univariate and multivariate Logistics regression. Four variables including BMI, serum total cholesterol, uric acid and proteinuria were selected as predictors in the nomogram development. A BTUP nomogram model was

successfully constructed and internally validated. This has been mentioned in previous studies.

Overweight is one of the risk factors of pregnancy-induced hypertension, and is closely related to the incidence of this disease [13]-[16]. Many studies have shown that pre-pregnancy overweight and obesity increase the prevalence of pregnancy-induced hypertension, and the risk of disease increases with the increase of BMI [17]-[19]. A retrospective cohort study found that the risk of HDP in overweight pregnant women was 1.99 times that of normal weight pregnant women. However, it is necessary to exclude pregnant women with chronic hypertension. This group of women has the greatest risk of HDP, but has nothing to do with obesity [20]. A prospective cohort study found that BMI ≥ 25 Kg/m^2 was associated with the risk of all types of HDP, and when BMI was used as a continuous variable and combined with other maternal characteristics, the best predictive performance for preeclampsia could be achieved [21]. In this study, multivariate logistic regression analysis showed that women with pre-pregnancy BMI ≥ 25 kg/m^2 had increased odds of HDP (OR = 3.231; 95% CI = 1.170 – 8.919), further confirming the previous study. The mechanism of the increased incidence of HDP caused by overweight is as follows: 1) Endothelial cell dysfunction increases the concentration of C-reactive protein and inflammatory cytokines, and secondary oxidative stress. 2) Adipocyte transition deposition affects placental development. 3) Activation of the complement system. 4) Endocrine metabolic disorders lead to increased peroxidase. 5) Leptin levels decrease. The above factors lead to vascular injury, contraction, platelet aggregation and atherosclerosis, eventually leading to increased blood pressure [17] [22]. It is recommended that overweight and obese women begin to take weight management measures, healthy diet, increase exercise, and control BMI during the pregnancy preparation stage. It is recommended that all pregnant women should plan and manage the weight during pregnancy from the early stage of pregnancy, strictly control the weight, pay close attention and monitor the blood pressure level to reduce the incidence of pregnancy-induced hypertension.

Generally maternal serum lipid levels are usually significantly elevated during pregnancy. However, pregnant women with pregnancy-induced hypertension often experience more remarkable serum lipid changes [23]. Many studies have found that pregnant women with pregnancy-induced hypertension often have dyslipidemia compared with normal pregnant women, such as increased TC, TG and LDL levels, and decreased HDL levels [24]-[27]. Wang *et al.* [28] found that the concentrations of serum TC, TG and LDL-C in the study group increased with the progression of pregnancy-induced hypertension. Shen *et al.* [29] found that in the early pregnancy, the levels of TC and LDL in the HDP group were higher than those in the normal group, but there was no significant difference in other periods. However, TG was higher in the HDP group throughout pregnancy. A multi-center prospective study found that TG, TC and LDH in first trimester were independently associated with hypertensive disorder complicating pregnancy

(HDCP), and the combination of blood lipid profile in first trimester with other common predictors can effectively improve the predictive ability of HDCP [30]. The results of this study showed that early pregnancy TG and TC in the HDP group were significantly higher than those in the CON group, and univariate logistic regression showed that both TG and TC could be used as independent influencing factors of HDP. (TG: OR = 4.596, TC: OR = 2.891). The role of dyslipidemia in the pathogenesis of pregnancy-induced hypertension is not yet clear. The possible mechanism is that hyperlipidemia produces excessive reactive oxygen, which in turn activates the RAAS system. This process, together with lipid peroxidation, causes endothelial dysfunction and ultimately leads to the occurrence of hypertension [31]. Adank *et al.* [32] also found that TG and TC were correlated with blood pressure during pregnancy, especially diastolic blood pressure.

In normal pregnancy, serum uric acid levels are usually reduced due to estrogen-induced uric acid excretion, increased renal blood flow, and increased glomerular filtration rate. In contrast, pregnant women with HDP had slightly higher serum uric acid levels during the first three months of pregnancy [3] [33]. Naina *et al.* [3] found that elevated serum uric acid levels in women with HDP usually occur before the onset of hypertension and proteinuria. There is a great correlation between maternal serum uric acid concentration and the occurrence of HDP, and it is considered to be a sign of the severity of HDP, which increases with the increase of maternal serum uric acid level. A case-control study found a positive linear relationship between elevated uric acid levels and preeclampsia. For each standard deviation increase in uric acid level, the adjusted odds ratio of preeclampsia was 1.21 (95%CI 1.11 – 1.33) [34]. The study also found that uric acid levels before 34 gestational weeks were more strongly associated with preeclampsia than between 34 and 37 weeks and after 37 weeks, but the confidence intervals of the three gestational age groups overlapped. Recent studies have also explored the possible mechanisms of uric acid-induced preeclampsia, including spiral artery remodeling caused by inhibition of NO production in endothelial cells, decreased trophoblastic integration due to internal antioxidant effects, and activation of inflammasome in trophoblast cells leading to the induction of inflammation at the maternal-fetal interface. All of the above lead to the occurrence of eclampsia to a certain extent [33]. Claudia *et al.* [34] concluded that the correlation between preeclampsia and elevated uric acid is not enough to support the identification of women with high risk of preeclampsia by uric acid alone. Therefore, our study adopted the method of combining uric acid with multiple risk factors and laboratory indicators of HDP to predict the risk of this disease. The results of this study showed that the level of uric acid in the third trimester was closely related to the occurrence of pregnancy-induced hypertension. For every standard deviation increase, the adjusted odds ratio of pregnancy-induced hypertension was 1.014(95%CI 1.008 - 1.020).

Proteinuria is a common manifestation in patients with eclampsia. Many

studies have shown that proteinuria during pregnancy is a good indicator for predicting and evaluating adverse maternal and infant outcomes [35] [36]. However, pregnant women with non-proteinuria PE may still develop severe adverse mother-infant outcomes. Therefore, even though proteinuria plays a vital role in assessing the severity of PE and mother-infant outcomes, it cannot be used as the only predictor [37]. The basic pathophysiology of eclampsia is systemic arteriolar spasm, which may lead to decreased renal perfusion and glomerular filtration rate. When the disease progresses, endothelial cells in the glomerular filtration barrier may be damaged, resulting in a large amount of protein loss and proteinuria [38]. Therefore, it is believed that the occurrence of proteinuria can be used as a potential indicator for predicting preeclampsia. The results of this study showed that proteinuria in the third trimester was closely related to the occurrence of HDP, and multivariate logistic regression analysis showed that pregnant women with proteinuria were 2.224 times more likely to have pregnancy-induced hypertension than those without proteinuria. A number of other studies have also shown that proteinuria is a predictor of the progression of gestational hypertension to preeclampsia [39] [40]. In addition, a retrospective study found that the maximal proteinuria can be used as a major predictor of the progression of eclampsia [41]. It is controversial whether proteinuria can be used as a necessary condition for the diagnosis of preeclampsia. The ASOG no longer uses proteinuria as a necessary diagnostic basis for eclampsia. The new guidelines stipulates that in the absence of proteinuria, preeclampsia can be diagnosed when the pregnant woman has a new-onset hypertension with any of the following symptoms including thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and headache [42]. There is another retrospective analysis found that proteinuria was not associated with the diagnosis of preeclampsia [43]. The possible explanation is that the symptoms of preeclampsia are multiple and non-specific. What's more, the incidence of preeclampsia patients is affected by many factors, hence the comprehensive analysis of proteinuria combined with other risk factors is more accurate in predicting HDP. Many studies have recommended retaining proteinuria as one of the monitoring indicators of preeclampsia, and using serial proteinuria assay to predict the progression of preeclampsia [36] [38] [44]. Besides, NICE guideline doesn't recommend repeating and following up the amount of proteinuria once the proteinuria has been detected [43]. Whether proteinuria should be used as one of the diagnostic criteria for preeclampsia needs further experimental design to prove.

The advantage of this study is that it combines risk factors and common laboratory indicators of HDP, and adopts logistics regression to determine the indicators included in the nomogram prediction model, which improves the accuracy of the model. In addition, the indicators finally included in the nomogram prediction model in this study are contained in the routine prenatal examination. This makes the data easy to obtain and provides convenience and feasibility for clinicians to use the prediction model in their work. On the other hand, this also

causes the model to lack specific indicators. Additionally, in order to ensure the integrity of the data, we used a random protein qualitative test instead of 24-hour proteinuria as a research indicator to study the relationship with HDP. This may lead to some false positive results. At the same time, this study was a single-center study with a relatively small sample size, and no further stratified analysis was performed on pregnant women in the HDP group. In future studies, more maternal characteristic indicators with high specificity and sensitivity, such as PIGF and sFLt-1, ultrasound indicators and clinical indications should be adopted. Based on this, a multi-center prospective randomized intervention trial should be carefully designed and to include a more representative population in a larger sample size. In order to improve the accuracy of the prediction model, conducting group studies on pregnant women with HDP and external tests to provide a reliable basis for clinical screening of HDP.

5. Conclusion

In conclusion, the BTUP nomogram model based on laboratory indicators and risk factors proposed in this study showed good predictive value for the risk assessment of HDP. These findings may provide a basis for the clinical identification of pregnant women with a high risk of HDP in advance.

Abbreviations

HDP: hypertensive disorders of pregnancy; BMI: body mass index; GDM: gestational diabetes; PCOS: polycystic ovarian syndrome; Fib: fibrinogen; D-D: D-Dimer; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactic dehydrogenase; TG: triglyceride; TC: total cholesterol; Lp(a): lipoprotein(a); Hb: hemoglobin; Plt: platelet; CRP: C-reactive protein.

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1) Data Availability Statement

The source data of the article is available upon request.

2) Competing Interests

The authors have declared that no competing interest exists.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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