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Combining multiaspect factors to predict the risk of childhood hypertension incidence

Jishuang Tong BS[1,#] | Xizhou An PhD[2,#] | Li Zhao PhD[1] | Ping Qu PhD[1] | Xian Tang MS[1] | Min Chen MNS[1] | Xiaohua Liang PhD[1]

[1]Clinical Epidemiology and Biostatistics Department, Children's Hospital of Chongqing Medical University, Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders, Key Laboratory of Pediatrics in Chongqing, China International Science and Technology Cooperation Center of Child Development and Critical Disorders, Chongqing, China

[2]Hematology and Oncology Department, Children's Hospital of Chongqing Medical University, Chongqing, China

Correspondence
Xiaohua Liang, 136, Zhong shan er lu Street, Yu zhong District, Chongqing 400014, China
Email: xiaohualiang@hospital.cqmu.edu.cn

[#]Xizhou An and Jishuang Tong have the same contribution.

Abstract

Childhood hypertension has become a global public health issue due to its increasing prevalence and association with cerebral-cardiovascular disease in adults. In this study, we developed a predictive model for childhood hypertension based on environmental and genetic factors to identify at-risk individuals. Eighty children diagnosed with childhood hypertension and 84 children in the control group matched by sex and age from an established cohort were included in a nested case–control study. We constructed a multiple logistic regression model to analyze the factors associated with hypertension and applied the 10-fold cross-validation method to verify the prediction stability of the model. Childhood hypertension was found positively correlated with triglyceride level ≥150 mg/dL; low-density lipoprotein cholesterol level ≥110 mg/dL; body mass index Z score; waist-to-height ratio Z score; and red blood cell count (all $P < .01$) and negatively correlated with the relative expression level of retinol acyltransferase; relative expression level of vitamin D receptor; and dietary intake of fiber, vitamin C and copper (all $P < .05$) in this study. BMI Z score, triglyceride ≥150 mg/dL, RBC count, VDR/β-actin and LRAT/β-actin ratios were used to construct the predictive model. The area under the receiver operating characteristic curve was 94.45% (95% CI = 89.35%~98.65%, $P < .001$). The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were all above 80% in both the training and validation sets. In conclusion, this model can predict the risk of childhood hypertension and could provide a theoretical basis for early prevention and intervention to improve the cardiovascular health of children.

KEYWORDS
case-control study, childhood, hypertension—general, prediction model

1 | INTRODUCTION

Essential hypertension (EH) imposes a serious disease burden worldwide, and its prevalence increases with age.[1] Childhood hypertension, defined as an average measured systolic (SBP) and/or diastolic blood pressure (DBP) ≥95th percentile after adjustment for age, sex and height,[2] has become a global public health issue of concern. According to the new clinical practice guidelines, the prevalence of childhood

hypertension was 17.85%.[3] Recent studies suggested that the prevalence of hypertension among Chinese children was more than 10%.[4] Previous studies found that childhood hypertension increased the risks of arterial stiffness,[5] high pulse wave velocity, high carotid intima-media thickness, left ventricular hypertrophy,[6] and onset of primary hypertension in adulthood,[5,7] which suggests that the pathogenesis of adult cerebral-cardiovascular disease (CCVD) originates in childhood, and the BP level in childhood is predictive for CCVD in adults. Thus, the development of predictive models to identify individuals at risk for childhood hypertension based on multi-aspect factors is critical.

Several hypertension predictive models for adults have been developed,[8,9] although most of these models include only anthropometric, socioeconomic and lifestyle variables. Predictive models including both genetic and environmental factors are limited. Previous studies illustrated that a variety of factors, including genetic,[10] socioeconomic,[11] dietary,[12,13] lifestyle,[13] and environmental factors,[14] impacted the incidence of childhood hypertension. However, no predictive model for EH in children has been reported until now, even though EH in children is a risk factor for adult CCVD.[5] Moreover, the measurement of BP and the diagnosis of EH in children are more complex than those in adults,[15] and the factors of feeding, which has been suggested to influence the incidence of childhood CVD,[16] might influence the incidence of EH, considering the specific situation of the child. Therefore, the development of predictive models for childhood EH based on risk factors from multiple dimensions, including environmental and genetic factors, is important for the identification of individuals at risk as early as possible and the development of prevention strategies targeting childhood EH. In the present study, we hypothesized that the risk factors for childhood hypertension could be used to develop a predictive model. To test this hypothesis, we first selected the determinants, which included demographic variables, socioeconomic status, dietary intake, lifestyle, physical activity, glucose-lipid metabolism indexes and routine blood test results. Second, the significant variables were used to establish a predictive model of hypertension in childhood. Third, validation of the model was performed using receiver operating characteristic (ROC) analysis. To our knowledge, this is the first EH predictive model for Chinese children.

2 | PARTICIPANTS AND METHODS

2.1 | Study population and sample size

The sample size was calculated with the formula $N_A = \frac{[Z_\alpha \sqrt{\{V_0(\hat{\Delta})\}} + Z_\beta \sqrt{\{V_A(\hat{\Delta})\}}]^2}{\Delta^2}$.[17] The parameters were designed to achieve 80% detection power. The difference between the area under the ROC curve (AUC) under the null hypothesis (0.80) and the AUC under the alternative hypothesis (0.88) was tested using a two-sided Z test with a significance level of 0.05. Discrete responses (1 = hypertension and 0 = control), false-positive rates between 1% and 10%, and the standard deviation (SD) of responses in the negative group versus that in the positive group was 0.330. A sample size of 82 in the positive and negative groups was needed. Thus, we selected 80 children in the hypertension group with randomized overall sampling and 84 children in the control group matched by sex and age. All participants were from a child health cohort established in 2014, which included 6102 children aged 6–12 years from six primary schools in an urban area of Chongqing. The inclusion criteria included the following: (1) 6~12 years old; (2) with no vitamin D (VD) supplementation or antihypertensive medication; (3) fulfilment of the diagnostic criteria in participants in the hypertensive group; (4) blood pressure levels lower than those specified in the diagnostic criteria based on sex, age, and height in control persons; and (5) informed consent forms were signed by the children and their guardians.

The exclusion criteria were as follows: (1) secondary hypertension, (2) hypertension with obvious clinical symptoms, (3) other diseases (eg, diabetes, CVD, or cancer) or dysfunction of the kidney that might influence BP, and (4) use of medications that influence blood pressure levels or VD metabolism. This study followed the guidance of the contents and supplements of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Children's Hospital of Chongqing Medical University. Written informed consent was obtained from all participants and their guardians.

2.2 | Demographic variables and nutrient intake

Demographic information, including sex, age, parents' education levels, average income of the family, birth weight, history of being breastfed and physical activity time, was obtained by the study coordinators through a comprehensive questionnaire. Total physical activity time was calculated by adding physical activity time at school and at home each day. A semiquantitative food frequency questionnaire described in a prior paper[11] was applied as the food intake survey. Moreover, daily food intake was converted into nutrients, and the daily intake amounts of energy, protein, fat, carbohydrate, fibre, retinol, vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin C, vitamin E, vitamin B6, vitamin B12, folate, niacin, calcium, iron, zinc, selenium, and copper were calculated according to the method described by Wu Zhiwei.[18]

2.3 | Anthropometric measurements

The doctors and nurses who carried out the anthropometric examinations were all pediatric specialists from Children's Hospital of Chongqing Medical University. They underwent rigorous training on use of the operation manual, which summarized the anthropometric examination guidelines recommended by the World Health Organization (WHO),[19] passed an examination before performing the anthropometric examinations and strictly followed the operation manual during the examinations. All anthropometric examinations strictly followed the operation manual during the physical examinations in this study. Automatic ultrasonic detectors (Ws-h300d) were used for height and weight measurements. The formula weight/(height*height) (kg/m^2) was used for body mass index (BMI) calculation. Waist circumference (WC) was measured twice in children who were fasted, wearing

close-fitting clothing, standing upright and relaxing the abdomen; the measurements were taken at the center of the navel at the end of exhalation without inhalation and averaged.

Height-for-age-specific Z scores (HAZs) and percentiles, weight-for-age-specific Z scores (WAZs) and percentiles, weight-for-height Z scores (WHZs) and percentiles, and BMI-for-age-specific Z scores (BMI-Zs) and percentiles were calculated using the SAS program provided by the Centers for Disease Control and Prevention.[20] WC-for-age Z scores (WCAZs) and WC/height-for-age Z scores (WHtRZs) were calculated using the formula Z score = ((value/M) *L-1)/(L*S) with the LMS parameters.[21]

BP was measured three times at 11, 13, and 15 minutes during a relaxation period of 15 minutes. The details of the measurements were described in our previous publication.[22] Two subsequent measurements were performed with a 1-week interval between each measurement when the BP of the first measurement exceeded the diagnostic criteria based on age, sex, and height. A hypertension diagnosis was made when the BP values of all measurements exceeded the diagnostic criteria. To exclude the effect of secondary hypertension, medical records of all the participants with hypertension were collected, and further anthropometric examinations were carried out by pediatric doctors.

2.4 | Biochemical indexes

Three milliliters of venous blood was drawn from each child after a 12-hour fast and no consumption of high-fat or spicy foods in the previous 24 hours in the morning. Automatic biochemical analyzers (Mindray BS-800) were used for blood fat and fasting blood glucose (FBG) detection. As described in detail in a previous publication,[23] VD levels were detected by high-performance liquid chromatography (HPLC). Automatic hematologic analyzers (Sysmex K-4500) were used to detect blood cell composition, including white blood cell (WBC) and red blood cell (RBC) counts; hemoglobin level; platelet counts; middle cell percentage of WBCs (W-MCR); small cell or lymphocyte count (W-SCC); large cell or neutrophil count (W-LCC); distribution width of RBCs (RDWSD); mean platelet volume (MPV); and the platelet-large cell ratio (P-LCR).

2.5 | RNA isolation and analysis

Total RNA was isolated from mononucleated cells in 2 mL peripheral blood. Two micrograms of total RNA were used as a template for retrotranscription to cDNA using the Prime Script® RT reagent kit (Takara, Japan) following the instruction manual. PCR primers for the VD receptor gene (VDR) (forward: GTCAGTTACAGCATCCAAAAGG and reverse: GACTCATTGGAGCGCAACATG) and lecithin retinol acyltransferase gene (LRAT) (forward: 5′GGAGGACTTCGCCTACGGA 3′ and reverse: 5′TTGTCGGACTGGGGACTGAT 3′) were designed. A SYBR II Premix Ex Taq TM (Takara, Japan) PCR system was used for the amplification of target genes. The reactions were run in a CFX Connect Real-Time PCR thermocycler (Bio Rad, USA). Reactions followed the protocol, with 40 cycles of denaturation at 95°C for 5 seconds and elongation at 60°C for 30 seconds. The specificity of primers was qualified by melting curve analysis for each gene in parallel. Each sample was quantified in triplicate. The relative expression levels of genes were calculated using the $2^{-\Delta\Delta Ct}$ method.[24] β-actin expression levels were used as internal controls and to normalize the expression levels with CFX Manager Software.

2.6 | Diagnostic criteria

The guidelines for hypertension diagnosis in our study have been described by Mi Jie and associates[2] and were established in accordance with the features of growth and development of Chinese children and adolescents. Furthermore, childhood hypertension was diagnosed as the average measured value of SBP and/or DBP ≥95th percentile for age, sex, and height. Dyslipidemia was defined as total cholesterol level ≥170 mg/dL and/or triglyceride level ≥150 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) level ≤40 mg/dL and/or low-density lipoprotein cholesterol (LDL-C) level ≥110 mg/dL according to the American Heart Association and the American Academy of Paediatrics Consensus statement.[25] In addition, abnormal FBG levels were defined as FBG ≥5.6 mmol/L.

2.7 | Statistical analysis

Continuous variables with a Gaussian distribution are presented as means ± SDs, and the independent sample t test was performed to compare differences between the hypertensive and control groups. Continuous variables with skewed distributions are presented as medians and interquartile ranges (M (P25-P75)), and the Mann–Whitney *U* test was performed to compare differences between the two groups. Categorical variables are presented as numbers and percentages [N (%)], and Pearson's $\chi 2$ test and Fisher's exact test were performed for intergroup comparisons. A multiple logistic regression model was used to analyze the related factors for hypertension and distinguish the two groups. A child was predicted to have hypertension when the probability was greater than or equal to 0.5 in the logistic regression model. The 10-fold cross-validation method was used to verify the stability of the prediction model. The AUC, accuracy (AC), sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) were calculated to evaluate the effect of prediction; values close to 1 represent a good effect. All statistical analyses were performed using SAS 9.4 software (Copyright 2016 SAS Institute Inc. Cary, NC, USA). Statistical significance was determined at $P < .05$.

3 | RESULTS

The demographic information, anthropometric variables, and socioeconomic statuses of the hypertensive and control groups were summarized in Table 1. First, compared to the control group, the hypertensive

TABLE 1 Difference of demographic characteristics between the hypertensive group and the control group

Variables	Total	Hypertension	Control	*P*
Age, years	9.81 ± 1.62	9.74 ± 1.77	9.89 ± 1.46	.56
Sex, no. (%)				
Male	83 (50.61)	42 (52.50)	41 (48.81)	.64
Female	81 (49.39)	38 (47.50)	43 (51.19)	
TET, min/day, no. (%)				
<150 min/week	77 (46.95)	36 (45.00)	41 (48.81)	.63
≥150 min/week	87 (53.05)	44 (55.00)	43 (51.19)	
Parents' education level, no. (%)				
<9 years	95 (57.93)	44 (55.00)	51 (60.71)	.34
~15 years	54 (32.93)	26 (32.50)	28 (33.33)	
>15 years	15 (9.15)	10 (12.50)	5 (5.95)	
The average household income, *Yuan*				
<1000	50 (30.49)	31 (38.75)	19 (22.62)	.08
1000~	73 (44.51)	31 (38.75)	42 (50.00)	
>3000	41 (25.00)	18 (22.50)	23 (27.38)	
Birth weight, g				
≤3000	44 (26.83)	18 (22.50)	26 (30.95)	.47
3001~3599	79 (48.17)	41 (51.25)	38 (45.24)	
≥3600	41 (25.00)	21 (26.25)	20 (23.81)	
Duration of breastfed, month, no. (%)				
<3	31 (18.90)	20 (25.00)	11 (13.10)	.15
3~9	84 (51.22)	38 (47.50)	46 (54.76)	
≥10	49 (29.88)	22 (27.50)	27 (32.14)	
BMI≥90th percentile, no. (%)	59 (35.98)	55 (68.75)	4 (4.76)	<.001
Height≥90th percentile, no. (%)	53 (32.32)	34 (42.50)	19 (22.62)	.007
Weight≥90th percentile, no. (%)	64 (39.02)	53 (66.25)	11 (13.10)	<.001
Waist≥90th percentile, no. (%)	28 (17.07)	27 (33.75)	1 (1.19)	<.001
BMI-Z	0.51 ± 1.41	1.39 ± 0.99	−0.33 ± 1.22	<.001
Height-Z	0.48 ± 2.13	1.13 ± 2.11	−0.14 ± 1.97	<.001
Weight-Z	0.50 ± 1.81	1.51 ± 1.35	−0.46 ± 1.67	<.001
Waist-Z	−0.21 ± 1.67	0.83 ± 1.28	−1.20 ± 1.38	<.001
WHtR-Z	−0.63 ± 1.68	0.28 ± 1.54	−1.49 ± 1.31	<.001

Abbreviations: BMI, body mass index; TET, total exercise time (at school and home); WHtR-Z, waist-to-height ratio.

group had a significantly higher BMI-Z, height, weight, WC, and WHtR (all $P < .001$). The percentages of BMI ≥90th percentile for age and sex, weight ≥90th percentile for age and sex, WC ≥90th percentile for age and sex (68.75% vs 4.76%, 66.25% vs 13.10%, 33.75% vs 1.19%, respectively, all $P < .001$), and height ≥90th percentile for age and sex (42.50% vs 22.62%, $P = .007$) in the hypertensive group were considerably higher than those in the control group.

Table 2 summarized the differences in the dyslipidemia rate, routine blood analysis results and nutrient intake between the hypertensive group and the control group. For dyslipidemia, the percentages of HDL-C ≤40 mg/dL, LDL-C ≥110 mg/dL and triglycerides ≥150 mg/dL were significantly higher in the hypertensive group than in the control group (13.75% vs 3.57%, 27.50% vs 7.14%, 35.00% vs 9.52%, respectively, all $P < .005$). For routine blood parameters, a higher WBC count, RBC count, and hemoglobin level were observed in children with hypertension than in the control persons (all $P < .01$). For dietary nutrition, fiber intake was significantly lower in the hypertension group than in the control group (31.92 ± 19.39 vs 25.80 ± 12.77, $P = .019$). Furthermore, compared to that in the control persons, the vitamin C level was significantly lower in children with hypertension ($P < .05$). Vitamin B6 and folate were marginally significantly different between the two groups ($P = .053$ and $P = .054$, respectively).

For dietary minerals, compared with that in the control group, copper intake was significantly lower in children with hypertension

TABLE 2 Difference of impact factors between the hypertensive group and the control group

Variables	Total	Hypertension	Control	*P*
Dyslipidemia				
Cholesterol≥170 mg/dL, no. (%)	41 (25.00)	23 (28.75)	18 (21.43)	.279
HDL-C≤40 mg/dL, no. (%)	14 (8.54)	11 (13.75)	3 (3.57)	.020
LDL-C≥110 mg/dL, no. (%)	28 (17.07)	22 (27.50)	6 (7.14)	.001
Triglycerides≥150 mg/dL, no. (%)	36 (21.95)	28 (35.00)	8 (9.52)	.001
GLU≥5.6 mmol/L, no. (%)	11 (6.71)	7 (8.75)	4 (4.76)	.307
Blood routine				
WBC > 10×10^9/L, no. (%)	10 (6.10)	9 (11.25)	1 (1.19)	.008
RBC < 5.5×10^9/L, no. (%)	14 (8.54)	10 (12.50)	4 (4.76)	.076
WBC, n$\times10^9$/L, no. (%)	7.05 ± 1.87	7.58 ± 1.91	6.55 ± 1.70	<.001
RBC, n$\times10^9$/L, no. (%)	4.93 ± 0.37	5.05 ± 0.37	4.82 ± 0.33	<.001
Hemoglobin, g/L	135.93 ± 9.11	138.46 ± 7.73	133.52 ± 9.71	<.001
Platelet, no.$\times10^9$/L	281.63 ± 73.74	289.79 ± 81.62	273.85 ± 64.90	.167
HCT, %	41.71 ± 2.66	41.55 ± 2.25	41.87 ± 3.00	.441
MCV, fL	84.89 ± 4.29	85.02 ± 4.52	84.76 ± 4.07	.701
MCH, pg	27.57 ± 1.70	27.70 ± 1.56	27.45 ± 1.83	.355
MCHC, g/L	325.90 ± 10.48	326.93 ± 11.59	324.92 ± 9.28	.221
WSCR, %	37.88 ± 8.20	38.38 ± 8.66	37.41 ± 7.77	.451
WMCR, no.$\times10^9$/L	5.63 ± 1.60	5.42 ± 1.51	5.83 ± 1.67	.101
WSCC, no.$\times10^9$/L	2.65 ± 0.68	2.63 ± 0.71	2.66 ± 0.66	.828
WMCC, no.$\times10^9$/L	0.42 ± 0.35	0.42 ± 0.49	0.41 ± 0.13	.800
WLCC, no.$\times10^9$/L	3.88 ± 1.50	3.69 ± 1.23	4.07 ± 1.69	.107
RDWSD, %	39.86 ± 3.01	39.44 ± 3.44	40.25 ± 2.48	.084
PDW, fL	13.68 ± 2.46	13.62 ± 2.32	13.74 ± 2.59	.762
MPV, fL	11.17 ± 1.15	11.20 ± 1.15	11.15 ± 1.16	.821
PLCR, %	33.45 ± 7.20	33.28 ± 7.10	33.61 ± 7.34	.769
Vitamin of serum				
Vitamin A, μmol/L	0.88 ± 0.23	0.83 ± 0.22	0.93 ± 0.23	.004
Serum 25(OH)D, μmol/L	40.81 ± 12.34	38.52 ± 12.00	43.00 ± 12.33	.020
Ratio (VDR/β-actin) $\times10^{-4}$/L	7.60 ± 3.06	7.11 ± 3.11	8.29 ± 3.45	.023
Ratio (LRAT/β-actin) $\times10^{-4}$/L	2.20 ± 2.17	1.27 ± 1.06	3.09 ± 2.56	<.001
Nutrition of dietary				
Energy, kcal	2411.4 ± 984.5	2310.7 ± 847.2	2507.2 ± 1096	.202
Protein, g	97.58 ± 53.48	92.38 ± 51.31	102.54 ± 55.32	.225
Fat, g	137.10 ± 63.86	131.33 ± 59.33	142.60 ± 67.79	.260
Carbohydrate, g	227.64 ± 109.7	218.18 ± 87.96	236.66 ± 127.0	.283
Fiber, g	28.93 ± 16.73	25.80 ± 12.77	31.92 ± 19.39	.019
Vitamin of dietary				
Vitamin A, μg RE	1211.1 ± 674.8	1150.5 ± 607.2	1268.8 ± 732.4	.263
Vitamin B1(Thiamin), mg	1.00 ± 0.49	0.93 ± 0.42	1.06 ± 0.54	.095
Vitamin B2(Riboflavin), mg	1.37 ± 0.72	1.32 ± 0.71	1.42 ± 0.73	.366
Vitamin C, mg	142.06 ± 92.72	126.12 ± 79.78	157.24 ± 101.7	.031
Vitamin E, mg	55.53 ± 28.89	52.72 ± 26.32	58.20 ± 31.07	.226
Vitamin B 6, mg	1.45 ± 0.75	1.33 ± 0.62	1.56 ± 0.84	.053

(Continues)

TABLE 2 (Continued)

Variables	Total	Hypertension	Control	*P*
Vitamin B12, Cobalamin, μg	11.97 ± 10.97	11.62 ± 12.59	12.30 ± 9.22	.691
Folate, μg	371.00 ± 210.2	338.66 ± 165.4	401.80 ± 242.5	.054
Niacin, mg	17.11 ± 10.53	16.07 ± 10.73	18.11 ± 10.30	.218
Minerals of dietary				
Calcium, mg	597.84 ± 280.3	581.46 ± 255.4	613.44 ± 302.8	.467
Iron, mg	16.95 ± 8.99	15.65 ± 7.56	18.19 ± 10.05	.070
Zinc, mg	15.25 ± 8.71	14.16 ± 8.26	16.28 ± 9.04	.118
Selenium, μg	62.88 ± 36.98	60.00 ± 35.30	65.62 ± 38.52	.332
Copper, mg	1.83 ± 1.27	1.56 ± 0.98	2.09 ± 1.46	.008

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GLU, glucose; WBC, white blood cell; RBC, red blood cell; HCT, red blood cell specific volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; W-SCR, WBC small cell ratio; W-MCR, WBC middle cell ratio or mixed cell percent; W-SCC, WBC small cell count or lymphocyte count; W-MCC, WBC middle cell count or mixed cell count; WLCC, WBC large cell count or neutrophil count; RDWSD, red blood cell distribution width-standard deviation; PDW, platelet distribution width; MPV, mean platelet volume; PLCR, platelet-large cell ratio; VDR, vitamin D receptor; LRAT, lecithin retinol acyltransferase.

(2.09 ± 1.46 vs 1.56 ± 0.98, $P = .008$). Moreover, the LRAT/β-actin ratio was significantly lower in the hypertension group ($P < .05$).

Table 3 summarizes the risk of hypertension in children. Regarding demographic information, an average household income of 1000–3000 yuan was positively associated with BP (model 1, $R^2 = 0.442$). For the growth and development indexes, the BMI-Z and WHtR were positively associated with BP (model 2, $R^2 = 0.546$). For dyslipidaemia, LDL-C ≥110 mg/dL and triglycerides ≥150 mg/dl were positively associated with BP, but HDL-C ≤40 mg/dL was negatively associated with BP (model 3, $R^2 = 0.217$). For routine blood test results, WBC and RBC counts were positively associated with BP (model 4, $R^2 = 0.24$). The VDR/β-actin and LRAT/β-actin ratios and fiber, vitamin C, and copper intake were negatively associated with BP (model 5, $R^2 = 0.368$; model 6, $R^2 = 0.046$; model 7, $R^2 = 0.038$; model 8, $R^2 = 0.059$). Overall, the BMI-Z (OR = 3.15, 95% CI = 1.886, 5.261, $P < .01$), triglycerides ≥150 mg/dL (hypertriglyceridemia, OR = 5.30, 95% CI = 1.279, 21.93, $P = .02$), and RBC count (OR = 9.69, 95% CI = 1.643, 57.18, $P = .01$) increased the odds of the development of hypertension, while an increased VDR/β-actin ratio (OR = 0.767, 95% CI = 0.645, 0.913, $P = .003$) and LRAT/β-actin ratio (OR = 0.611, 95% CI = 0.495, 0.755, $P < .01$) reduced the odds of developing hypertension (model 9, $R^2 = 0.714$).

The ROC curve of Model 9 for the prediction of hypertension in children was shown in Figure 1, and the AUC was 94.45% (95% CI = 89.35%~98.65%, $P < .001$).

The formula for prediction of the probability of hypertension in children is as follows:

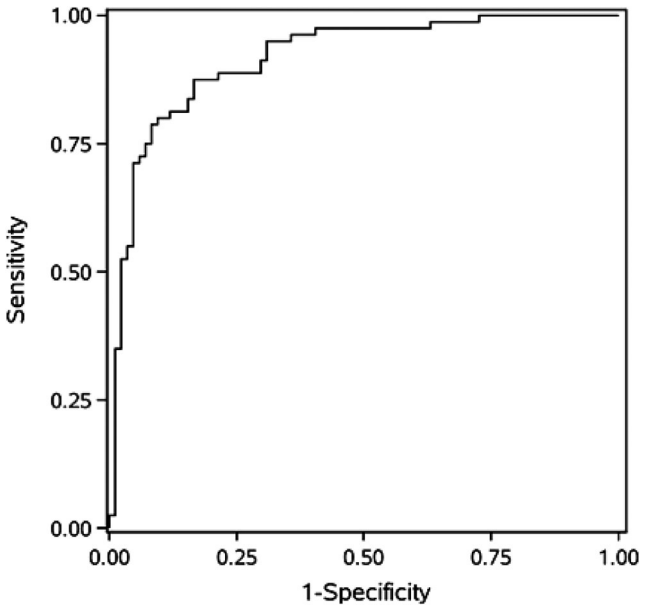

FIGURE 1 ROC curve of Model 9 for the prediction of hypertension in children

Children were judged to have hypertension when the probability was greater than or equal to 0.5 in model 9, with an accuracy of 86.60% (95% CI = 81.37%, 91.80%), a sensitivity of 87.50% (95% CI = 80.25%, 94.75%), a specificity of 85.71% (95% CI = 78.23%, 93.20%), a PPV of 85.37% (95% CI = 77.72%, 93.02%), and a NPV of 87.80% (95%

$$P = \frac{e^{1.1475BMIZ+1.667triglyceride\geq 150mg/dl+2.2714RBC-0.265VDR/\beta-actin-0.492LRAT/\beta-actin}}{1+e^{1.1475BMIZ+1.667triglyceride\geq 150mg/dl+2.2714RBC-0.265VDR/\beta-actin-0.492LRAT/\beta-actin}} \quad (1)$$

TABLE 3 The risk factors of children with hypertension in logistic regression model

model	β	SE	OR (95%CI)	P	R^2
Model 1[†]					
Family income, Yuan/per month					
<1000			1.0(reference)		
1000~	0.509	0.234	2.085 (0.900, 4.832)	.029	0.442
>3000	−0.284	0.213	0.943 (0.436, 2.041)	.182	
Model 2[‡]					
BMI-Z	1.209	0.242	3.352 (2.086, 5.386)	<.001	0.546
WHtR-Z	0.402	0.155	1.496 (1.103, 2.028)	.009	
Model 3[§]					
HDL-C≤40 mg/dL	−1.589	0.692	0.204 (0.053,0.793)	.022	0.217
LDL-C≥110 mg/dL	1.357	0.519	3.884 (1.403,10.75)	.009	
Triglyceride≥150 mg/dL	1.341	0.462	3.822 (1.543,9.464)	.004	
Model 4[♯]					
WBC, no.×10^9/L	0.275	0.107	1.317 (1.067, 1.626)	.010	0.24
RBC, no.×10^9/L	2.086	0.597	8.057 (2.500, 25.97)	<.001	
RDWSD, %	−0.176	0.077	0.839 (0.720, 0.977)	.024	
Model 5[††]					
VDR/β-actin	−0.215	0.065	0.806 (0.710, 0.916)	.001	0.368
LRAT/β-actin	−0.402	0.072	0.669 (0.580, 0.771)	<.001	
Model 6[‡‡]					
Fiber, g	−0.024	0.010	0.976 (0.956, 0.997)	.022	0.046
Model 7[§§]					
Vitamin C, mg	−0.004	0.002	0.996 (0.993, 1.000)	.035	0.038
Model 8[♯♯]					
Copper, mg	−0.356	0.138	0.701 (0.534, 0.919)	.010	0.059
Model 9[†‡]					
BMI-Z	1.147	0.261	3.150 (1.886, 5.261)	<.001	0.714
Triglyceride≥150 mg/dL	1.667	0.725	5.296 (1.279, 21.93)	.021	
RBC, no.×10^9/L	2.271	0.905	9.693 (1.643, 57.18)	.012	
VDR/β-actin	−0.265	0.088	0.767 (0.645, 0.913)	.003	
LRAT/β-actin	−0.492	0.108	0.611 (0.495, 0.755)	<.001	

*Variables are chosen by the stepwise method.

[†]Choose from age, sex, and demographic information, which include total exercise time (at school and home), parents' education level, the average household income.

[‡]Choose from age, sex and growth and development index which include birth weight, duration of breastfed, the Z-score of BMI, Z-score of height, Z-score of weight, Z-score of waist, and Z-score of WHtR.

[§]Choose from age, sex and dyslipidaemia which include cholesterol≥170 mg/dL, HDL-C≤40 mg/dL, LDL-C≥ 110 mg/dL, triglyceride≥150 mg/dL, GLU≥5.6 mmol/L.

[♯]Choose from age, sex, and blood routine which include WBC, RBC, hemoglobin, platelet, WMCR, WSCC, WLCC, RDWSD, MPV, PLCR.

[††]Choose from age, sex, and serum VA, serum 25(OH)D, 25(OH)D receptor, and LRAT.

[‡‡]Choose from age, sex, and nutrition of dietary, which include energy, protein, fat, carbohydrate, fiber.

[§§]Choose from age, sex, and vitamin of dietary, which include vitamin A, vitamin B1, vitamin C, vitamin E, vitamin B6, vitamin B12, folate, niacin.

[♯♯]Choose from age, sex, and minerals of dietary which include calcium, iron, zinc, selenium, copper.

[†‡]Choose from age, sex, and variables which $P < .05$ in model 1 to model 8. (the average household income, BMI Z-score, Z-score of WHtR, HDL-C≤40 mg/dL, LDL-C≥110 mg/dL, triglyceride ≥150 mg/dL, WBC, RBC, RDWSD, VDR/β-actin, fibre, vitamin C, LRAT/β-actin, copper).

TABLE 4 The predicted result of 10-fold cross-validation from ROC models

Indexes of ROC models	Train set	Validation set
ROC area, %(95%CI)	94.49(93.97, 95.02)	93.39(88.65, 98.13)
Accuracy, %(95%CI)	86.72(85.98, 87.47)	84.23(76.5, 91.96)
Sensitivity, %(95%CI)	88.05(87.2, 88.89)	83.32(71.68, 94.95)
Specificity, %(95%CI)	85.42(84.06, 86.77)	85.42(74.91, 95.92)
PPV, %(95%CI)	85.24(84.31, 86.17)	85.78(76.79, 94.77)
NPV, %(95%CI)	88.24(87.39, 89.09)	82.34(69.85, 94.82)

Abbreviations: NPV, negative predictive values; PPV, positive predictive values; ROC, receiver operator characteristic curve.

CI = 80.72%, 94.89%). The accuracy, sensitivity, specificity, PPV, and NPV were above 80% in both the training and validation sets (Table 4). There were few differences in the accuracy, sensitivity, specificity, PPV, and NPV between the training set and validation set.

4 | DISCUSSION

A predictive model for hypertension in children was presented in our study; the model elucidated the risk factors for the development of hypertension in children. A multivariate logistic regression model was used to predict the risk of childhood hypertension and included the variables BMI-Z, triglyceride level ≥150 mg/dL, RBC count, VDR expression level, and LRAT expression level, with an R^2 of 0.714. Furthermore, the 10-fold cross-validation method was applied to validate the predictive model.

In our study, the BMI-Z and a high level of triglycerides (≥150 mg/dL) were confirmed to be significant predictors of hypertension in children. Most children and adolescents with obesity had a high level of triglycerides,[26] which has been confirmed in other studies to be a risk factor for childhood hypertension.[27] Our study confirmed that the risk of hypertension increased approximately two fold for each 1-SD increase in BMI, consistent with previous studies that found that overweight and obesity increased the risk of hypertension by two-fold.[28] Another study showed that among overweight or obese children who were not obese in adulthood, the risk of the development of hypertension was similar to that among those who had never been obese.[29] It is possible that short-term obesity does not lead to changes in vascular structure and function,[30] suggesting that weight control in children with obesity should receive extra attention to be the target of interventions to prevent cardiovascular damage in adulthood.

In previous studies, the peripheral RBC count and hemoglobin level have been found to be risk factors for hypertension in children.[31] In our study, we consistently concluded that the RBC count and hemoglobin concentration were independent risk factors for hypertension among children. The mechanism between RBCs and hypertension has been investigated in only a few studies, and the activity of Na-K ATPase and cell deformability[32] were thought to contribute to hypertension. Additionally, the RDW has been demonstrated to be a risk factor for morbidity of and mortality due to CVDs.[33] In our study, we did not measure the stiffness or deformability of RBCs, but the results did not show a difference in RDW between the normal and hypertensive children. Moreover, the RBC count in peripheral blood was found to be significantly higher in children with hypertension. Considering that RBCs affect hemodynamic parameters and blood volume,[34] it is possible that hemodynamic and blood volume changes due to RBC count differences were the underlying mechanism by which hypertension was induced.

Hypertension has a complex pathogenesis, and genetic factors are important contributors to its development.[10] This is the first study to confirm that VDR expression was associated with a lower incidence of childhood hypertension. Controversial results showed that VDR expression did not play a role in the regulation of BP, probably because low serum calcium affects BP levels.[35] Therefore, the results need to be further validated. A meta-analysis confirmed that the VDR BsmI gene polymorphism was associated with the pathogenesis of hypertension.[36] VDR is widely distributed in vascular endothelial cells and vascular smooth muscle cells,[37] and VDR deficiency has been shown to trigger impaired acetylcholine-induced aortic diastolic function and decreased phosphorylated vasodilator-stimulated phosphoprotein levels.[38] VDR deficiency also results in decreased bioavailability of the vasodilator NO and decreased expression of endothelial NO synthase, leading to endothelial dysfunction, increased arterial stiffness, and increased aortic impedance. It further affects vascular tone and thus regulates BP.[39] Another study showed that knockdown of the VDR gene increased renin expression.[40] The increase in renin synthesis led to an increase in plasma Ang II levels produced by angiotensinogen because Ang II is an effective vasoconstrictor, and the increase in Ang II levels led to the development of hypertension.[40,41]

LRAT, an enzyme localized on the endoplasmic reticulum that catalyzes the esterification of all-trans-retinol into all-trans-retinyl ester, plays a key role in vitamin A metabolism. In this study, the relative LRAT expression level was identified as an independent risk factor for the occurrence of hypertension, which was consistent with the results of our previous study.[42] However, there was little evidence of the relationship between serum vitamin A levels and hypertension. In our previous study, we found that low LRAT expression was relevant to both vitamin A deficiency and high BP in children and that LRAT may affect BP levels by decreasing angiotensin-converting enzyme (ACE) levels.[42] However, no significant relationship was found between the serum vitamin A level and BP,[43] which was consistent with the results of a randomized clinical trial performed by Agustin Llopis-González and colleagues.[44] In a previous study, LRAT was found to be a key molecule in retinol metabolism by which holo-RBP activated the STRA6/JAK/STAT signal cascade,[45] and this signal cascade has been associated with BP control.[41] Ang II is a strong vasoconstrictor and contributes to the development of hypertension. The JAK-STAT pathway is involved in the transcription of the angiotensin II gene. Furthermore, IL-6 and STAT3 enhance the expression of angiotensinogen, resulting in an increase in Ang II levels.[41] LRAT inhibited the activity of STRA6, thereby suppressing the regulation of BP by the STRA6-mediated cellular signal cascade response.[46] These findings suggested

a complicated mechanism between LRAT expression and hypertension other than retinol metabolism.

Dietary balance is considered an important factor that influences the occurrence of hypertension in adults. In these studies, sodium, fat and sugar were the most concerning nutrients. In our study, the levels of LDL-C, HDL-C, triglycerides, and glucose in serum were all significantly higher in the hypertension group, which suggested consistency with these studies. In addition to these nutrients, dietary fiber, and vitamin C levels were significantly lower in children with hypertension in this study. Although these nutrient factors have seldom been included in predictive models for hypertension, their roles have been mentioned in hypertension animal model and patient cohort studies.[47,48] Vitamin C can reduce the concentration of inflammatory cytokines and proteins in the serum of hypertensive patients,[49] and supplementation with vitamin C showed a significant reduction effect on BP in hypertensive patients.[50] Fiber and its metabolites prevented the development of hypertension, and the underlying mechanism might be due to improvement of the gut microbiota structure after fiber supplementation, which has been demonstrated in a mouse model.[48]

Cumulating evidence has shown that leukocytes are associated with the initiation of hypertension; however, studies on the relationship between hypertension and WBCs have mostly been conducted in adults,[51–53] and few studies have been conducted in children. In 2008, Tatsukawa and associates[53] found that an elevated WBC count was associated with an increased risk of hypertension. In 2015, Liu and associates[54] further identified the neutrophil-to-lymphocyte ratio (NLR) as a predictor of hypertension. A preclinical study elucidated that leukocytes influenced vascular inflammation, which further promoted the occurrence of hypertension. Reactive oxygen species (ROS) in circulating blood leukocytes can activate signal transduction pathways for gene expression and protein modification, resulting in increased vascular tone as well as vascular remodeling and microvascular inflammation.[55] ROS and inflammatory factors can also influence the interaction between endothelial cells and leukocytes, which can cause vascular dysfunction and further induce hypertension.[56] Additionally, a study showed that the hydrodynamic interaction of slower-moving leukocytes with erythrocytes led to a disruption in their position in the capillaries, resulting in an increase in apparent viscosity and capillary resistance, which in turn affected BP.[57]

Compared with other studies, the present study included more potentially relevant candidate predictors, analyzing not only demographic variables, socioeconomic status, dietary intake, lifestyle factors, physical activity time, glucose-lipid metabolism indexes, and routine blood test results but also genetic factors. The present model included both genetic and environmental factors, and an internal validation was conducted in this study. This model was one of the few models to predict the risk of hypertension in childhood. There are five limitations of this study. First, the participants in our study were aged 6 to 12 years, so validation of the model in other age groups was needed; second, our study did not take parental BP into account, though hypertension has been found to be related to genetic factors. A future study will measure parental BP to validate our model. Third, this model was constructed based on a case–control study, which did not demonstrate the etiology of hypertension. Fourth, dietary vitamins were calculated from dietary intake, which may be impacted by recall bias. Fifth, only internal validation with no external validation was performed. Therefore, cohort studies with follow-up data are needed to further evaluate the performance of this model.

In conclusion, our study strengthens the understanding of the relationship between childhood risk factors and childhood hypertension and emphasizes the importance of promoting and maintaining ideal BP levels during childhood. Application of the model allows early screening of children at risk for cardiovascular disease and the administration of preventive measures and treatments. Validation and optimization of existing models are still needed in future studies to improve the performance of the model.

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CONFLICT OF INTERESTS

All authors of this manuscript declare that they have no known competing financial interests or personal relationships that could lead to the conflict of interests.

AUTHOR CONTRIBUTION

XA and JT performed the experiments and wrote the paper; LZ, PQ, XT, and MC participated in the anthropometric measurements and analyzed the data; XL conceived and designed the experiments; and all the authors critically reviewed and approved the final paper.

ORCID

Xiaohua Liang PhD https://orcid.org/0000-0003-3867-9779

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