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A Nomogram model for the early warning of essential hypertension risks based on the principles of traditional Chinese medicine syndrome elements

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ABSTRACT

Objective To construct a Nomogram model for the prediction of essential hypertension (EH) risks with the use of traditional Chinese medicine (TCM) syndrome elements principles in conjunction with cutting-edge biochemical detection technologies.

Methods A case-control study was conducted, involving 301 patients with essential hypertension in the hypertensive group and 314 without in the control group. Comprehensive data, including the information on the four TCM diagnoses, general data, and blood biochemical indicators of participants in both groups, were collected separately for analysis. The differentiation principles of syndrome elements were used to discern the location and nature of hypertension. One-way analysis was carried out to screen for potential risk factors of the disease. Least absolute shrinkage and selection operator (LASSO) regression was used to identify factors that contribute significantly to the model, and eliminate possible collinearity problems. At last, multivariate logistic regression analysis was used to both screen and quantify independent risk factors essential for the prediction model. The “rms” package in the R Studio was used to construct the Nomogram model, creating line segments of varying lengths based on the contribution of each risk factor to aid in the prediction of risks of hypertension. For internal model validation, the Bootstrap program package was utilized to perform 1 000 repetitions of sampling and generate calibration curves.

Results The results of the multivariate logistic regression analysis revealed that the risk factors of EH included age, heart rate (HR), waist-to-hip ratio (WHR), uric acid (UA) levels, family medical history, sleep patterns (early awakening and light sleep), water intake, and psychological traits (depression and anger). Additionally, TCM syndrome elements such as phlegm, Yin deficiency, and Yang hyperactivity contributed to the risk of EH onset as well. TCM syndrome elements liver, spleen, and kidney were also considered the risk factors of EH. Next, the Nomogram model was constructed using the aforementioned 14 risk predictors, with an area under the curve (AUC) of 0.868 and a 95% confidence interval (CI) ranging from 0.840 to 0.895. The diagnostic sensitivity and specificity were found to be 80.7% and 85.0%, respectively. Internal validation confirmed the model’s robust predictive performance, with a

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consistency index (C-index) of 0.879, underscoring the model's strong predictive ability.
Conclusion By integrating TCM syndrome elements, the Nomogram model has realized the objective, qualitative, and quantitative selection of early warning factors for developing EH, resulting in the creation of a more comprehensive and precise prediction model for EH risks.

1 Introduction

Essential hypertension (EH) has emerged as one of the prevailing chronic conditions worldwide, and ranks as the foremost risk factor for the onset of cardiovascular and cerebrovascular diseases. Additionally, it stands as one of the principal contributors to mortality and deterioration of physiological functions [1, 2]. Therefore, the early detection, prevention, and management of EH have evolved into pivotal endeavors within the realm of healthcare management in China. Currently, prediction models for EH risks primarily rely on biochemical indicators [3-7]. However, these models often overlook the evaluation of the functional state of internal organs and the implementation of personalized traditional Chinese medicine (TCM) preventive and therapeutic strategies. TCM, with its holistic approach, offers a comprehensive assessment of an individual's well-being, and is poised to personalized early warning and intervention measures for disease. The TCM syndrome elements encompass both the disease's location and its inherent nature, which is fundamental in TCM diagnosis. These elements not only capture the current disease state, but also offer insights into its evolving trajectory [8]. Their ability to predict the onset of diseases aligns well with the contemporary demands of advancing TCM through their quantitative and objective attributes. Therefore, this study integrated the principles of TCM syndrome elements to construct a more pragmatic and intuitive Nomogram model for EH prediction, and aimed at furnishing a TCM diagnostic foundation for the early warning, prevention, and treatment of EH.

2 Data and methods

2.1 Research objective

This study recruited participants from the physical examination center of the Second People's Hospital Affiliated to Fujian University of Traditional Chinese Medicine, consisting of 301 EH patients as the hypertensive group, and 314 non-hypertensive individuals as the control group. This research was conducted in strict compliance with ethical and moral principles (Ethical approval number: SPHFJP-Y2022124-01).

2.2 Diagnostic criteria

2.2.1 Diagnostic criteria for EH The diagnostic criteria for EH were established in accordance with the Chinese Hypertension Prevention and Treatment Guidelines 2018 Revised Edition and Guideline for the Pharmacological Treatment of Hypertension in Adults [9, 10]. Hypertension was defined as systolic blood pressure $\geqslant$ 140 mmHg and/or diastolic blood pressure $\geqslant$ 90 mmHg in the absence of antihypertensive medication use, or as individuals with a previous history of hypertension currently on antihypertensive medication.

2.2.2 Diagnostic criteria for syndrome elements Drawing from ZHU Wenfeng's work on *Syndrome Element Dialectics* [8], the identification elements were determined with the use of the weighted threshold method, guided by the weights assigned to the four TCM diagnoses. Each symptom's severity was taken moderate as the baseline, with a quantitative diagnostic value adjusted to 1.5 when the symptom was deemed severe and scaled down to 0.7 for lighter symptoms. Based on the cumulative scores calculated for each syndrome element, a four-tiered classification was employed, with the scores below 70 fell into level 0, indicating the absence of pathological changes; scores ranging from 70 to less than 100 as level 1, signifying the presence of mild pathological changes; scores from 100 to less than 150 as level 2, indicating the presence of moderate pathological changes; and scores equal to or greater than 150 as level 3, suggesting the presence of severe pathological changes.

2.3 Inclusion and exclusion criteria

2.3.1 Inclusion criteria Patients were included if: (i) they met the aforementioned diagnostic criteria; (ii) they were aged between 18 and 80 years; (iii) they had independent civil rights; (iv) they could make their own decisions whether to participate in this study; (v) their informed consent forms were collected.

2.3.2 Exclusion criteria Patients were excluded if: (i) they had secondary hypertension; (ii) they were complicated with tumors or serious pathological changes in heart, liver, kidney or other organs; (iii) they had acute or chronic respiratory diseases; (iv) they were pregnant or in lactation; (v) their clinical data were incomplete.

2.4 Data collection

Data in the study were collected from the Chinese Hypertension Prevention and Treatment Guidelines 2018 Revised Edition and Guideline for the Pharmacological

Treatment of Hypertension in Adults with the integration of the EH risk factors obtained from our team's prior study on the prediction of chronic disease risks carried out through expert consultation [9, 11], and from the four TCM diagnoses, general physical examinations, biochemical indicators, and questionnaires as well. (i) TCM syndrome elements mainly included phlegm, dampness, heat, cold, Yang hyperactivity, Yang deficiency, Yin deficiency, wind, blood stasis, Qi stagnation, blood deficiency, Qi deficiency, fluid deficiency, liver, heart, spleen, lung, kidney, gallbladder, small intestine, stomach, large intestine, and heart spirit. (ii) General data included height, weight, blood pressure, waist circumference, and hip circumference. (iii) Biochemical indicators encompassed fasting plasma glucose (FPG), direct bilirubin (DBIL), indirect bilirubin (IBiL), lactate dehydrogenase (LD), creatinine (CRE), uric acid (UA), globulin (GLB), albumin (ALB), apolipoprotein A1 (APOA1), apolipoproteins B (APOB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), creatine kinase (CK), urea, triacylglycerol (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), white blood cell count (WBC), red blood cell count (RBC), Hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), potassium (K), chloride (Cl), calcium (Ca), phosphorus (P), magnesium (Mg), sodium (Na), percentage of polymorphonuclear leukocytes (POP), percentage of polymorphonuclear neutrophils (NE), lymphocytes (LY), monocytes (MONO), eosinophils (EO), and basophils (BASO). (iv) Questionnaires included inquiries regarding family medical history, lifestyle habits (such as smoking, alcohol consumption, water intake, and exercise), and psychology.

2.5 Statistical analysis

Categorical variables were presented as frequencies (in percentages), while continuous variables were presented as mean ± standard deviation (SD). The chi-square test was employed for the analysis of dichotomous and unordered categorical variables. For continuous variables that did not follow a normal distribution, the two independent samples rank-sum test was employed. The two independent samples *t* test was applied for data conforming to normal distribution. Ordered categorical variables were assessed using the two independent samples rank-sum test as well. Following this, the least absolute shrinkage and selection operator (LASSO) regression analysis was performed using the "glmnet" package in the R 4.1.3 language to identify relevant covariates. Subsequently, a multivariate logistic regression model was used to analyze the factors influencing EH. To construct the Nomogram model for the prediction of EH risks, the "rms" package was utilized. The model's performance was evaluated using the area under the receiver operating characteristic curve (AUC). For internal model validation, the Bootstrap program package was used to perform 1 000 repetitions of sampling and generate calibration curves. Differences were considered statistically significant at $P < 0.05$.

3 Results

3.1 Univariate analysis of general data of patients in the hypertensive and control groups

Table 1 reveals noteworthy disparities between the hypertensive group and the control group in various aspects, including gender, age distribution, waist-to-hip ratio (WHR), body mass index (BMI), education, family medical history, smoking habits, sleep patterns, water intake, sweet consumption, and psychology ($P < 0.05$).

3.2 Univariate analysis of biochemical indicators of patients in the hypertensive and control groups

Table 2 illustrates a significant difference in osmolality, GLB, ALT, AST, TG, TC, HDL-C, LDL-C, APOB, FPG, LD, CRE, UA, Mg, WBC, RBC, Hb, and MCHC of patients between the two groups ($P < 0.05$).

3.3 Analysis of the distribution of TCM syndrome elements

Table 3 presents a comparative analysis of the TCM syndrome elements between the hypertensive group and the control group. Regarding the syndrome elements related to the nature of the disease, statistical differences were observed for phlegm, dampness, heat, Yang hyperactivity, and Yin deficiency between the two groups ($P < 0.05$). Additionally, among the syndrome elements associated with the location of the disease, statistically significant differences were noted for the liver, heart, spleen, kidney, and stomach ($P < 0.05$) between the two groups.

3.4 EH risk factor screening

Figure 1 depicts the coefficient solution path generated using the LASSO regression analysis, with each line symbolizing a variable. The vertical axis represents the parameter coefficients, while the horizontal axis denotes the fractional deviation interpretation and $\log(\lambda)$. Distinct $\log(\lambda)$ values are associated with the selection of varying numbers of variables, and the variables featuring non-zero coefficients are the outcomes of the LASSO screening process. Figure 2 shows the results of the LASSO regression analysis to determine the optimal tuning parameter λ. As λ varies, the degree of compression applied to the

Table 1 Univariate analysis of the general data

Group	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	HR (BPM)	Gender		Age distribution			WHR		BMI			
				Male (= 1)	Female (= 2)	Youth (= 1)	Middle-aged (= 2)	Elderly (= 3)	Normal (= 1)	Abnormal (= 2)	Thin (= 1)	Normal (= 2)	Overweight (= 3)	Obese (= 4)
Hypertensive group (n = 301)	152.29 ± 10.39	91.50 ± 9.13	77.49 ± 11.23	173	128	43	138	120	58	243	2	111	137	51
Control group (n = 314)	121.50 ± 9.91	75.94 ± 7.31	74.44 ± 10.17	151	163	84	168	62	139	175	8	186	102	18
$t/\chi^2/Z$ value	37.600	23.380	− 3.009	5.431		34.401			44.112		− 6.530			
P value	< 0.001	< 0.001	0.003	0.02		< 0.001			< 0.001		< 0.001			

Group	Educational attainment				Family medical history		Smoking habit		Drinking wine		Exercise		Sleep pattern			
	Illiteracy (= 1)	Primary School diploma (= 2)	Junior high school diploma (= 3)	High school and above (= 4)	No (= 0)	Yes (= 1)	Yes (= 1)	No (= 2)	Yes (= 1)	No (= 2)	Yes (= 1)	No (= 2)	Normal (= 1)	Difficulty falling asleep (= 2)	Early awakening (= 3)	Light sleep (= 4)
Hypertensive group (n = 301)	42	57	106	97	118	183	102	199	102	199	163	138	108	86	57	50
Control group (n = 314)	39	38	70	167	205	109	71	243	93	221	190	124	176	66	31	41
$t/\chi^2/Z$ value	29.513				46.298		9.665		0.038		2.540		27.223			
P value	< 0.001				< 0.001		0.002		0.246		0.111		< 0.001			

Group	Water intake				Sweets consumption				Psychology				
	Often (= 1)	Occasionally (= 2)	Rarely (= 3)	Never (= 4)	Often (= 1)	Occasionally (= 2)	Rarely (= 3)	Never (= 4)	None (= 1)	Anxiety (= 2)	Depression (= 3)	Anger (= 4)	Tension (= 5)
Hypertensive group (n = 301)	147	86	68	0	54	65	136	46	102	46	33	103	17
Control group (n = 314)	191	66	57	0	44	49	150	71	141	53	26	73	21
$t/\chi^2/Z$ value	− 2.753				2.880				12.850				
P value	0.006				0.004				< 0.001				

Table 2 Univariate analysis of the biochemical indicators

Group	ALB (g/L)	GLB (g/L)	DBIL (μmol/L)	I BIl (μmol/L)	ALT (U/L)	AST (U/L)	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)
Hypertensive group (n = 301)	44.27 ± 2.55	30.76 ± 3.89	5.29 ± 2.56	9.60 ± 4.49	27.77 ± 18.51	22.95 ± 9.28	1.85 ± 1.06	5.41 ± 1.09	1.26 ± 0.30
Control group (n = 314)	44.15 ± 3.00	29.80 ± 3.44	5.06 ± 1.74	8.91 ± 3.90	22.99 ± 18.30	20.69 ± 8.89	1.40 ± 0.86	5.03 ± 0.88	1.33 ± 0.37
Z value	– 0.540	– 2.938	– 0.363	– 1.809	– 5.073	– 4.341	– 6.836	– 4.473	2.823
P value	0.589	0.003	0.716	0.071	< 0.001	< 0.001	< 0.001	< 0.001	0.005

Group	LDL-C (mmol/L)	APOA1 (g/L)	APOB (g/L)	FPG (mmol/L)	LD (U/L)	CK (U/L)	Urea (mmol/L)	CRE (μmol/L)	UA (μmol/L)
Hypertensive group (n = 301)	3.27 ± 0.91	1.43 ± 0.25	1.13 ± 0.25	5.79 ± 1.57	200.14 ± 29.85	116.14 ± 66.75	5.11 ± 1.22	73.48 ± 13.58	388.88 ± 92.59
Control group (n = 314)	2.95 ± 0.74	1.44 ± 0.26	1.00 ± 0.22	5.32 ± 0.88	189.66 ± 30.71	112.88 ± 59.44	5.00 ± 1.28	70.33 ± 12.62	348.03 ± 91.88
Z value	– 4.324	0.861	– 6.149	– 5.567	– 3.998	– 1.017	– 1.225	– 3.114	– 5.747
P value	< 0.001	0.389	< 0.001	< 0.001	< 0.001	0.304	0.221	0.002	< 0.001

Group	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Mg (mmol/L)	P (mmol/L)	Na (mmol/L)	POP (mosm/L)	WBC (*10^9/L)	NE (%)
Hypertensive group (n = 301)	4.20 ± 0.62	105.35 ± 5.06	2.33 ± 0.11	0.86 ± 0.07	1.07 ± 0.16	141.09 ± 2.00	292.27 ± 7.53	6.50 ± 1.61	55.40 ± 8.53
Control group (n = 314)	4.21 ± 0.30	105.45 ± 1.89	2.32 ± 0.09	0.87 ± 0.29	1.08 ± 0.15	140.84 ± 1.84	291.86 ± 4.58	6.12 ± 1.53	54.92 ± 7.92
Z value	1.791	1.824	– 1.612	– 2.694	0.471	– 1.208	– 2.245	– 3.223	1.060
P value	0.073	0.068	0.107	0.007	0.637	0.227	0.025	0.001	0.291

Group	LY (%)	MONO (%)	EO (%)	BASO (%)	RBC (*10^9/L)	Hb (g/L)	MCV	MCH	MCHC	RDW
Hypertensive group (n = 301)	35.45 ± 8.74	6.05 ± 1.37	2.37 ± 1.63	0.62 ± 0.27	4.86 ± 0.48	144.85 ± 14.36	91.24 ± 4.62	29.81 ± 2.05	326.94 ± 10.73	12.66 ± 0.86
Control group (n = 314)	36.05 ± 7.41	6.08 ± 1.36	2.39 ± 2.18	0.60 ± 0.29	4.74 ± 0.54	140.35 ± 14.10	91.34 ± 6.10	29.70 ± 2.45	324.71 ± 10.50	12.67 ± 1.20
Z value	– 1.353	– 0.294	0.801	0.830	– 3.217	– 3.610	– 1.455	0.015	2.958	2.259
P value	0.176	0.769	0.423	0.407	0.001	< 0.001	0.146	0.988	0.003	0.024

Table 3 Univariate analysis of TCM-related influencing factors

Group	Phlegm				Dampness				Heat				Cold			
	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)
Hypertensive group (n = 301)	144	70	65	22	164	56	48	33	208	43	35	15	229	25	30	17
Control group (n = 314)	224	39	41	10	203	30	53	28	253	22	21	18	248	29	29	8
χ^2/Z value			− 5.746				− 2.033				− 2.974				− 1.069	
P value			< 0.001				0.042				0.003				0.285	

Group	Yang hyperactivity				Yang deficiency				Yin deficiency				Wind			
	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)
Hypertensive group (n = 301)	184	51	41	25	219	42	22	18	144	85	58	14	252	23	23	3
Control group (n = 314)	258	18	20	18	235	37	28	14	235	41	28	10	248	28	28	10
χ^2/Z value			− 5.421				0.554				− 6.547				1.595	
P value			< 0.001				0.580				< 0.001				0.111	

Group	Blood stasis				Qi stagnation				Blood deficiency				Qi deficiency			
	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)
Hypertensive group (n = 301)	221	44	25	11	212	39	30	20	220	45	27	9	216	43	25	17
Control group (n = 314)	249	32	22	11	244	26	22	22	225	41	36	12	223	46	27	18
χ^2/Z value			− 1.597				− 1.844				0.589				0.198	
P value			0.110				0.065				0.556				0.843	

Group	Fluid depletion				Stomach				Large intestine				Heart spirit			
	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)
Hypertensive group (n = 301)	182	73	35	11	190	50	38	23	241	31	27	2	199	42	39	21
Control group (n = 314)	214	55	35	10	233	31	30	20	264	18	30	2	225	40	32	17
χ^2/Z value			− 1.748				− 2.715				− 1.132				− 1.552	
P value			0.080				0.007				0.258				0.121	

Group	Liver				Heart				Spleen				Lung			
	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)
Hypertensive group (n = 301)	203	52	39	7	205	45	39	12	133	77	70	21	185	75	36	5
Control group (n = 314)	251	29	30	4	241	42	23	8	208	52	38	16	208	65	39	2
χ^2/Z value			− 3.366				− 2.572				− 5.306				− 1.128	
P value			0.001				0.010				< 0.001				0.259	

Group	Kidney				Gallbladder				Small intestine			
	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)	None (= 0)	Mild (= 1)	Medium (= 2)	Heavy (= 3)
Hypertensive group (n = 301)	133	80	69	19	213	36	40	12	230	39	29	3
Control group (n = 314)	221	44	34	15	241	33	31	9	244	41	25	4
χ^2/Z value			− 6.187				− 1.751				− 0.422	
P value			< 0.001				0.080				0.673	

model's variables and the number of selected variables undergo alterations. The results indicated that the model's error reached its minimum point at log(λ) = – 3.582 317, resulting in the selection of 26 variables, including age, heart rate (HR), BMI, WHR, GLB, TG, TC, APOB, FPG, UA, MCHC, RDW, education, family medical history, smoking habits, sleep patterns, water intake, sweet consumption, psychology, the syndrome elements of phlegm, Yang hyperactivity, Yin deficiency, liver, spleen, kidney, and stomach.

3.5 Multivariate logistic regression analysis

The potential risk factors identified through the LASSO regression analysis were employed as independent variables in a multivariate logistic regression analysis. As presented in Table 4, several factors emerged as independent risk factors for EH, including age (middle-aged and elderly participants), WHR abnormality, HR, UA, family medical history, water intake, psychological traits (depression and anger), sleep patterns (early awakening and light sleep), TCM syndrome elements related to the nature of the disease (phlegm, Yin deficiency, and Yang hyperactivity), and syndrome elements associated with the location of the disease (liver, spleen, and kidney) (P < 0.05).

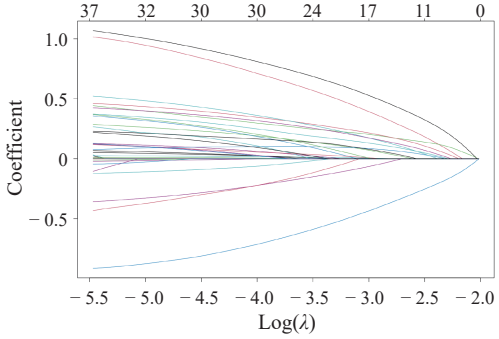

Figure 1 The LASSO regression analysis path of the coefficients

Different colored lines represent different characteristics.

3.6 Establishment and evaluation of the Nomogram model

The Nomogram model was established employing the independent risk factors identified through the

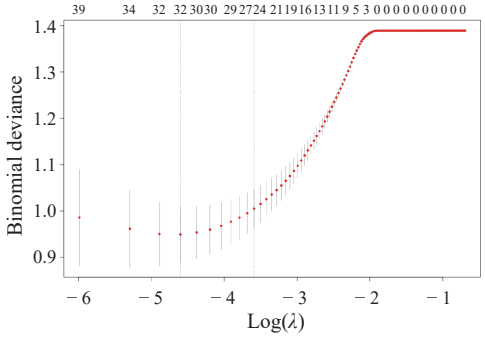

Figure 2 The Cross validation of the LASSO regression analysis

Table 4 Multivariate logistic regression analysis of factors influencing EH

Risk factor		β	SE	Wald	P value	OR	95% CI
Age distribution	Middle-aged	1.032	0.343	9.063	0.003	2.806	1.433-5.492
	Elderly	2.037	0.386	27.899	< 0.001	7.667	3.601-16.327
Syndrome elements	Phlegm	0.408	0.136	9.056	0.003	1.504	1.153-1.961
	Yin deficiency	0.537	0.135	15.909	< 0.001	1.710	1.314-2.226
	Yang hyperactivity	0.300	0.136	4.829	0.028	1.349	1.033-1.763
	Liver	0.465	0.157	8.796	0.003	1.591	1.171-2.163
	Spleen	0.547	0.133	16.989	< 0.001	1.727	1.332-2.240
	Kidney	0.492	0.131	14.101	< 0.001	1.636	1.265-2.116
Sleep pattern	Early awakening	0.942	0.370	6.495	0.011	2.566	1.243-5.296
	Light sleep	0.876	0.357	6.015	0.014	2.402	1.192-4.840
Psychology	Depression	1.185	0.433	7.507	0.006	3.271	1.401-7.637
	Anger	0.610	0.288	4.472	0.034	1.840	1.046-3.239
WHR		1.090	0.302	13.076	< 0.001	2.976	1.648-5.374
HR		0.031	0.012	6.902	0.009	1.032	1.008-1.056
UA		0.004	0.001	5.597	0.018	1.004	1.001-1.006
Family medical history		1.140	0.243	21.955	< 0.001	3.128	1.941-5.040
Water intake		0.716	0.316	5.135	0.023	2.046	1.102-3.802

β (Beta): regression coefficient represents the relationship between the predictor variables and the response variable. SE (standard error): SE of the estimate, indicates the variability or uncertainty in the regression coefficient. Wald: Wald statistic is a measure used for testing the significance of the coefficients in the logistic regression model. P value: P value determines the significance of the regression coefficients and is a measure of the probability that the observed results occurred by chance; OR (odds ratio): OR measures the association between the predictor variables and the outcome variable. 95% CI (95% confidence interval): 95% CI provides a range within which the true value of the population parameter is likely to fall.

multivariate logistic regression analysis (Figure 3). To obtain the corresponding score of each independent variable, a vertical line was drawn from the axis of that variable to the "Points" axis. The total score was determined by summing up the "Points" values assigned to each variable. The total points were calculated by aggregating the respective "Points" values for each variable, following which the corresponding value on the "Total points" axis was located. Lastly, a vertical line extending to the bottom axis labeled "prevalence of hypertension" was drawn, and the value where the line intersects the axis represents the probability of developing the disease. The discrimination capability of the model was assessed using the receiver operating characteristic (ROC) curve, yielding an AUC of 0.868 and a 95% CI ranging from 0.840 to 0.895, with a diagnostic sensitivity of 80.7% and a specificity of 85%. These results, as depicted in Figure 4, affirmed the model's excellent discriminative performance. The model underwent internal validation through 1 000 repetitions employing the Bootstrap method, resulting in a consistency index (C-index) of 0.879. Furthermore, the calibration curve demonstrated a high level of agreement between the actual predicted probability curve, the ideal curve, and the calibration curve. These findings, as depicted in Figure 5, underscored the model's accuracy in prediction of EH risks.

4 Discussion

4.1 Risk factors of EH and construction of its model

EH, a prevalent cardiovascular condition, poses significant risks beyond elevated blood pressure levels. Of greater concern is its potential to cause long-term damage or impairment to vital organs. EH also stands as an independent risk factor for adverse cardiovascular and cerebral vascular events, such as heart failure, cardiac arrhythmia, stroke, and even sudden death [12]. Our team has carried out extensive researches into the theory and application of the early signs of developing EH [11, 13-16]. However, our primary approach centered only on the utilization of the scales for early signs of EH risks, which had

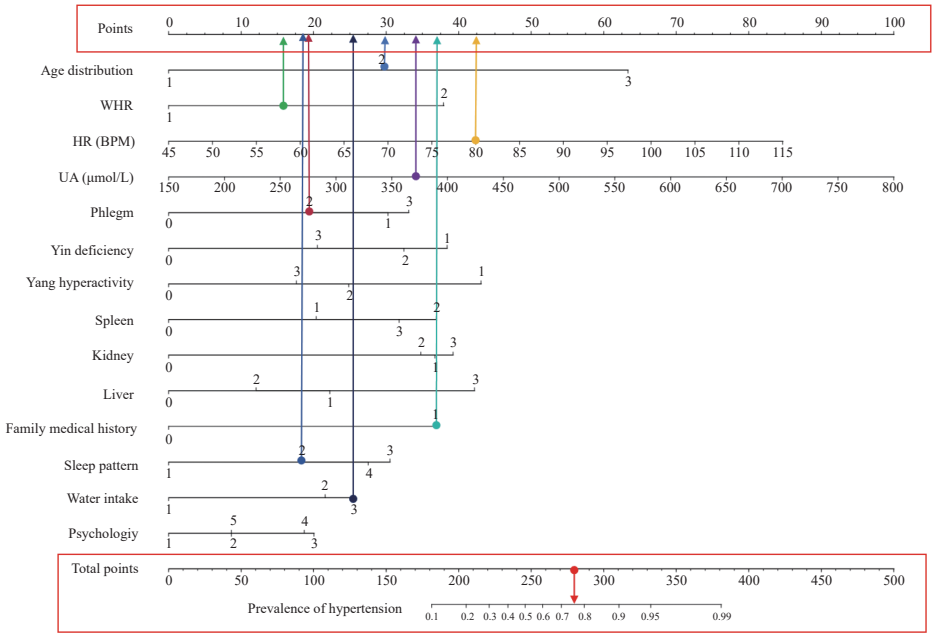

Figure 3 Prediction results from the Nomogram model for the risks of EH onset

HR, WHR, and UA are shown as coordinate lines with actual observations, and TCM evidence, age distribution, family history, sleep patterns, water intake, and psychological factors are shown as coordinate lines with categorical assigned values.

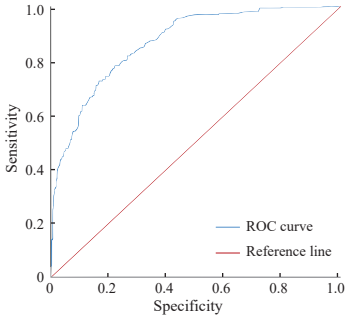

Figure 4 ROC curve of the Nomogram model

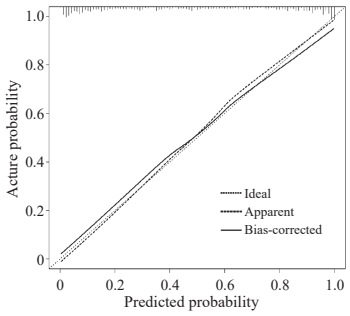

Figure 5 Calibration curve of the Nomogram model

its drawbacks, including a cumbersome assessment process and a lack of visual clarity in presenting the results, leading to the hindrance of its widespread adoption and practical application in clinical settings. Building upon prior research on the risk factors of EH, this study conducted an in-depth screening of the associated factors, including TCM factors. Subsequently, an innovative Nomogram model was constructed for the prediction of the EH risks, integrating a diverse array of indicators, all aimed at enhancing the effectiveness of EH risk prediction.

A multivariate logistic regression analysis was performed as well in the study, following variable screening through the LASSO regression analysis. LASSO, a model grounded in the penalty function, adeptly compresses regression coefficients while preserving the benefits of subset shrinkage. It effectively addressed the challenge of covariance among model variables [17, 18]. The results of the multivariate logistic regression analysis also showed that the risk of EH elevated with the increase of age, abnormal WHR, elevated HR and UA, the presence of family medical history, insufficient water intake, early awakening or light sleep, depression, and anger.

4.2 Analysis of biochemical indicators and behavioral risk factors in EH

The results also demonstrated that EH arose from a multifaceted interplay of various factors. In particular, the middle-aged population exhibited a 1.806-fold increase in the risk of EH (OR = 2.806, 95% CI: 1.433 - 5.492), while the elderly population showed a substantial 6.667-fold increase in the risk of EH (OR = 7.667, 95% CI: 3.601 - 16.327), when compared with the risk observed in the young population. It is known that as individuals transition into old age, their susceptibility to EH will experience a remarkable upsurge. This phenomenon can largely be attributed to the natural aging process, which entails the progressive stiffening and diminishes elasticity of blood vessels. Meanwhile, there is a gradual decline in sympathetic nerve activity, which results in a weakening of the body's self-regulatory mechanisms of the blood pressure. This complex interplay ultimately contributes to a heightened risk of developing EH [19]. Therefore, bolstering systems for early signs and prevention strategies for EH among the elderly population promises significant health benefits. Furthermore, the study unveiled a notable influence of genetic factors in the progression of EH, underscoring that individuals with a familial predisposition to EH faced a 2.128-fold higher likelihood of developing the condition compared with those without family history of EH (OR = 3.128, 95% CI: 1.941 - 5.040). A study of the genetic associations of blood pressure in more than 1 million Europeans has identified 535 new blood pressure sites, not only providing new biological insights into blood pressure regulation, but also highlighting a common genetic structure between blood pressure and lifestyle exposure [20].

In this study, it was observed that an abnormal WHR emerged as a noteworthy risk factor of EH. Interestingly, WHR demonstrated greater sensitivity in the EH model when compared with BMI. WHR is frequently utilized as an indicator of central obesity, suggesting that individuals with central obesity tendencies are particularly susceptible to EH. According to TCM principles, there is often a discernible link between one's body shape and constitution, which can provide valuable insights into an individual's predisposition to specific diseases to some extent [21]. Meanwhile, the results also showed that among the biochemical indicators examined, only UA emerged as a significant risk factor for EH. Notably, each incremental unit increase in UA value corresponded to a 0.004-fold increase in the risk of EH (OR = 1.004, 95% CI: 1.001 - 1.006). UA serves as the end product in the catabolism and metabolism of purine compounds within the human body. Elevated levels of UA signal abnormalities in metabolic functions, making it a crucial prediction indicator for the onset of EH [22]. According to pertinent studies, heightened UA levels were implicated in the development of EH through diverse ways. The primary mechanisms involved encompass oxidative stress, inflammatory response, activation of the renin-angiotensin system, and the inhibition of carbon monoxide synthesis [23]. Therefore, the daily management of dietary purine intake stands as a crucial preventive measure for individuals at risk of the EH onset. In addition, it's worth noting that this study did not incorporate smoking and alcohol consumption into the Nomogram model for EH prediction. Recent Mendelian randomization meta-analyses reported that smoking might be associated with hypertension [24]. Research in China and outside explored the association between alcoholic beverages and cardiovascular diseases, albeit with inconclusive findings. Some studies observed that residents in certain regions who consumed homemade wine had a tradition of using it for cold protection, disease prevention, and overall health maintenance. Additionally, studies suggested that some alcohols might have the effects of lowering blood pressure [25-28]. Nonetheless, epidemiological surveys suggest that both smoking and alcohol consumption tend to elevate the risk of EH and its associated complications [29, 30]. Therefore, it remains imperative to continue efforts on health education focused on smoking cessation and alcohol moderation among the population.

4.3 Analysis of risk factors of TCM syndrome elements

The study results revealed that risk factors of EH in relation to TCM syndrome elements encompassed imbalances such as phlegm, Yin deficiency, and Yang

hyperactivity, as well as issues related to the liver, spleen, and kidney. These results highlighted the intricate nature of EH development, representing a complex pathological state characterized by dys-regulation across multiple internal organ functions. Of these factors, "phlegm" is predominantly classified as an inflammatory factor in contemporary medical research. For instance, YANG et al. [31] contended that individuals with phlegm-dampness obstruction might experience chronic inflammation, potentially contributing to endothelial inflammatory injury and angiogenesis. It was regarded as one of the foremost factors implicated in the onset and progression of EH [31]. Furthermore, *Thousand Golden Prescriptions* (*Qian Jin Fang*, 《千金方》) advanced the perspective that "phlegm-heat was intricately associated with wind, and this interplay between wind and the heart led to a condition termed "wind dizziness" [32]. Therefore, it is evident that phlegm can serve as a trigger for the onset of EH and its characteristic clinical symptoms, and it is a pivotal mechanism underlying vascular endothelial dysfunction in hypertensive conditions. In this study, both Yin deficiency and Yang hyperactivity were jointly considered as risk factors for EH. WANG et al. [33] reported that individuals characterized by Yin deficiency and Yang hyperactivity were at a heightened risk of prehypertension progressing into full-blown hypertension. The hyperactivity of the body's Yang is frequently attributed to the deficiency of Yin and bodily fluids within the liver and kidney. Yin deficiency results in the inability to regulate Yang, leading to the hyperactivity of liver Yang. In the present study, the liver was found to be a risk factor for EH, a finding that aligns with the ancient wisdom found in *Plain Question* (*Su Wen*, 《素问》), which asserts that "all winds and dizziness originate from the liver". In addition, the liver exhibits a close connection with emotional fluctuations, and notably, emotional dys-regulation plays a pivotal role in the pathogenesis of hypertension [34]. This observation conforms to the results in this study regarding psychological attributes, specifically anger and depression, which are identified as risk factors consistent with this emotional dimension. It is also unveiled in the study that the spleen is one of the significant risk factors for EH. EH was observed with the ability to precipitate by dietary irregularities, excessive exertion, or indulgence, which could harm the spleen. Consequently, Yin deficiency in the spleen and dampness may ensue, ultimately giving rise to the accumulation of heat over time, leading to the formation of phlegm [35]. The central mechanism at play involves internal organ dysfunction and the irregular movement of Qi, with the spleen and stomach serving as the focal points for regulating this vital Qi movement. Therefore, equal attention should be directed towards both the liver and spleen in the prevention of EH in TCM. The essence of this approach lies in the regulation and harmonization of Qi, with the ultimate aim of restoring the equilibrium of Yin and Yang within the human body. Kidney-related factors also emerged as significant risk factors for EH. This association arose from the natural physiological decline in kidney essence that accompanied the aging process. Moreover, the interplay of inherent attributes, dietary choices, emotional well-being, physical exertion, and desires, contributed to a weakening of the kidney's regulatory capabilities [36]. This, in turn, prompted the dysfunction of renal Qi, impacting its ability to "warm" and "moisten" the pulse pathway. Subsequently, this impairment led to abnormalities in vascular function and structure, marking the inception of hypertensive vascular endothelial dysfunction.

5 Conclusion

The study has developed a comprehensive visual EH risk warning model that incorporates multiple objective indicators, including physiological, metabolic, genetic, and TCM factors. This model allows for the objective, qualitative, and quantitative selection of warning factors. This model visually demonstrates the weights and relationships of various factors. Internal validation indicates that it aligns closely with actual observed values, and ROC curves confirm its high discriminative power. It possesses a certain level of scientific validity and reliability, and underscores the significant role of the TCM concept of "preventive treatment of disease" in disease risk prediction. This research provides support and guidance for the application of TCM in the prevention and treatment of EH.

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Competing interests

The authors declare no conflict of interest.

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基于中医证素原理构建原发性高血压病风险预警 Nomogram 模型

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【摘要】目的 基于中医证素原理，结合现代生物化学检测技术，探讨原发性高血压病的危险因素，从而构建原发性高血压病风险预警模型。**方法** 采用病例对照研究，原发性高血压 301 例为高血压组，非原发性高血压 314 例为对照组。分别采集两组人群的中医四诊信息、一般资料和血液理化指标等信息。采用证素辨证方法获取病位证素和病性证素。采用单因素分析初步筛选潜在的危险因素，利用最小绝对收缩和选择算子（LASSO）回归以识别对模型具有显著贡献的因素，并消除可能存在的共线性问题，运用多因素 logistic 回归分析筛选并量化预测模型的独立危险因素；应用 R Studio 的“rms”包构建 Nomogram 模型，该模型根据各危险因素贡献程度的大小分别形成长短不同的线段，以帮助预测患高血压病的风险；对于模型内部验证，利用 Bootstrap 程序包进行 1 000 次重复采样，并绘制校准曲线。**结果** 多因素 logistic 分析结果显示，原发性高血压病危险因素包括年龄、心率（HR）、腰臀比（WHR）、尿酸（UA）水平、家族史、睡眠情况（早醒、浅睡）、饮水量和心理特征（抑郁、急躁）等。此外，痰、阴虚和阳亢等中医病性证素也增加了 EH 发病的风险，中医病位证素肝、脾和肾也被认为是 EH 的危险因素。利用以上 14 个风险预测指标构建了 Nomogram 模型，其曲线下面积（AUC）= 0.868（95% CI: 0.840~0.895），诊断灵敏度、特异性分别为 80.7%、85.0%，内部验证得到一致性指数（C-index）为 0.879，提示该模型具有较好的预测能力。**结论** 融合了中医证素的 Nomogram 模型，实现了预警因素的客观、定性、定量化选择，从而构建了一种更为全面和准确的原发性高血压病风险预警模型。

【关键词】 原发性高血压病；中医；证素；危险因素；预警模型；治未病