




Development of a nomogram for screening the risk of left ventricular hypertrophy in Chinese hypertensive patients

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Abstract

Left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular morbidity and mortality in hypertensives. Therefore, early identification of at-risk patients is necessary. The objective of this study was to estimate the risk of LVH among Chinese hypertensives by designing a nomogram. 832 hypertensives were divided into two groups based on the presence of LVH. The least absolute shrinkage and selection operator (LASSO) regression and multivariable logistic regression were successively applied for optimal variable selection and nomogram construction. Discrimination power, calibration, and clinical usefulness were evaluated using the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis. Internal validation was performed using the bootstrap method. The nomogram included five predictors, namely gender, duration of hypertension, age, body mass index (BMI), and systolic blood pressure. The area under the ROC curve (AUC) was 0.724 (95% CI: 0.687-0.761), indicating moderate discrimination. The calibration curve showed an excellent agreement between the predicted LVH and the actual LVH probability. The risk threshold between 5% and 72% according to the decision curve analysis, and the nomogram is clinically beneficial. Internal validation by bootstrapping with 1000 samples showed a good C-index of 0.715, which suggested that the predictive abilities for the training set and testing set were in consistency. Our study proposed a nomogram that can be utilized to assess the LVH risk rapidly for Chinese hypertensives. This tool could be useful in identifying patients at high risk for LVH. Further studies are required to ascertain the stability and applicability of this nomogram.

1 | INTRODUCTION

Hypertension is the leading risk factor for cardiovascular diseases and premature mortality worldwide.¹ Recent global trends showed that the prevalence of hypertension has decreased in high-income countries, but increased in low- and middle-income countries.² The Status of Hypertension in China published in 2018 revealed that the

prevalence of hypertension in Chinese adults is 23.2% and is gradually rising.³ Left ventricular hypertrophy (LVH) is a common complication of hypertension and is a key mediator between the risk factors and the cardiovascular events.⁴ It has been reported that multiple factors, such as blood pressure level, age, obesity, gender, the severity of hypertension, and dietary salt intake, are involved in the development of LVH.⁵

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The development of LVH is a complicated interaction of mechanism underlying hypertension. An accurate prediction model identifying patients at high risk of LVH in the early stages might be useful in the prevention of cardiovascular events. Until now, only a small number of prediction models for left ventricular mass have been reported.⁶⁻⁹ However, most of these models were designed using the Caucasian populations. Previous studies have proposed that ethnic disparities in the prevalence of LVH exist.^{10,11} In addition, there might also be ethnic differences regarding the relationship between LVH and poor cardiovascular outcomes.^{12,13} Existing evidence suggests that the relationship between LVH and poor cardiovascular outcomes is strongest among Chinese and Hispanics compared with non-Hispanic Whites.¹³ This could imply that Chinese and Hispanics might benefit more from a risk prediction model for LVH. Nevertheless, to the best of knowledge there are no LVH risk prediction models aimed at Chinese hypertensives.

The aim of this study was to use routine clinical measures to develop a predictive model for LVH in Chinese hypertensives and to convert the complex predictive formula into an intuitive nomogram, which can be utilized to assess the LVH risk rapidly in the clinical setting.

2 | METHODS

2.1 | Ethics statement

This study adhered to the guidelines outlined in Helsinki Declaration, and the Ethics Board of the First Affiliated Hospital of Fujian Medical University provided the ethical approval. All study subjects completed an informed consent.

2.2 | Study population

This survey was conducted as a single-center, cross-sectional study. The study protocol was developed prior to clinical data acquisition and implemented by experienced clinicians. Overall, 1951 hypertensive patients aged between 18 and 90 years were recruited from the department of Geriatrics and General Medicine in the First Affiliated Hospital of Fujian Medical University, during the period beginning January 2016 to March 2019. The exclusion criteria were as follows: (a) incomplete medical records; (b) secondary hypertension and serious cardiovascular diseases; (c) acute myocardial infarction and cerebrovascular accident within the past three months; (d) serious liver or kidney diseases; (e) autoimmune diseases and malignancy; (f) active inflammatory or infectious diseases; and (g) pregnancy. According to the exclusion criteria described above, 832 patients were finally enrolled.

2.3 | Survey and measurements

All participants completed the structured questionnaires, which contained detailed demographic information regarding gender, age,

smoking habits, and previous medical history in the consultation room at their first visit.

The height and body mass were measured in patients with light-weight clothing and without shoes. Body mass index (BMI) constituted the ratio calculated by dividing body mass (in kilograms) by squared height (in meters). Blood pressure was measured using an automatic blood pressure monitor (Omron, Kyoto Japan) after patients were requested to rest for 5 minutes in a seated position.

Blood samples for biochemical testing were collected via venipuncture after no less than 8 hours overnight fasting and then analyzed using a fully automatic biochemistry analyzer (ADVIA 2400 Chemistry System, Siemens). The methods have been described before.¹⁴⁻¹⁹ Briefly, serum creatinine levels were measured using an enzymatic method.¹⁴⁻¹⁹ Serum uric acid, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol levels were analyzed via the oxidase method.¹⁴⁻¹⁹ The estimated glomerular filtration rate (eGFR) was assessed by the modification of diet in renal disease (MDRD) formula: $eGFR [mL / (min \cdot 1.73 m^2)] = 186 \times [serum\ creatinine\ (mmol/L) \times 0.0113]^{-1.154} \times (Age)^{-0.203}$, and adjustments for gender were 1 for male and 0.742 for female.²⁰ Glycosylated hemoglobin was determined using ion-exchange high-performance liquid chromatography (HPLC).^{14,15,17} Urinary albumin was assessed via turbidimetric immunoassay. Urinary creatinine was measured by the colorimetric method. The urinary albumin-to-creatinine ratio (UACR) was calculated as urinary albumin divided by urinary creatinine and expressed in milligrams per gram.^{14,15,17}

Echocardiography was performed by a well-trained sonographer blinded to the clinical details. All measurements were carried out as previously described.¹⁷ Briefly, images were obtained with the patient in the supine left decubitus position. M-mode tracings were employed to measure LV end-diastolic dimension (EDD) and septal wall thickness (SWT) and posterior wall thickness (PWT). The left ventricular mass (LVM) was calculated based on the formula: $0.8 \times 1.04 \times [(EDD + SWT + PWT)^3 - EDD^3] + 0.6$.²¹ Body surface area (BSA) was calculated from height and bodyweight: $0.006 \times \text{height (in centimeters)} + 0.0128 \times \text{bodyweight (in kilograms)} - 0.1529$. The LVM index (LVMI) was calculated by dividing LVM by the BSA.

2.4 | Definitions

Hypertension was defined as blood pressure > 140/90 mmHg or having known hypertension or self-reported antihypertensive therapy.^{22,23} Diabetes was defined as a new diagnosis of diabetes or self-reported history of diabetes or self-reported use of hypoglycemic agents according to the guideline provided by the American Diabetes Association in 2014.²⁴ Current smokers were defined as individuals who smoked at least 100 cigarettes during their lifetimes and currently smoke cigarettes every day.²⁵ According to the American Society of Echocardiography guidelines, LVH was defined as LVMI > 115 g/m² and > 95 g/m² for males and females, respectively.²¹

2.5 | Statistical Analysis

All statistical analyses were conducted using Statistical Product and Service Solutions (version 20.0) and R software (version 4.0.2; <https://www.R-project.org>). The measurement data were tested for normal distribution (Kolmogorov-Smirnov test) and homogeneity of variance (Levene's test). Continuous variables were described by means \pm standard deviations or median and interquartile distance. Categorical variables were expressed as percentages (%) and absolute numbers (n). Variables between groups were assessed by chi-square test and Student's t test as appropriate. To select the best potential predictive variables, the least absolute shrinkage and selection operator (LASSO) regression was performed using the "glmnet" package of R software.²⁶ To obtain the best subset of predictors, the LASSO regression minimizes the error in prediction for a response variable by placing a penalty constraint to the model that forces regression coefficients for some variables toward zero. By implementing LASSO regression, variables with nonzero coefficients remain in the final model. Based on $-2\log$ -likelihood test, 10-fold cross-validation was carried out by LASSO regression for centralization and standardization of included variables and then obtains the best-fit lambda value. The lambda with 1 standard error provides a simplest model with good performance and is used for variable selection. These variables were then taken into multivariate logistic regression model. After multivariate analysis, the independent predictors were chosen to develop a nomogram. The "rms" package of R software was utilized to create the nomogram. The discrimination efficiency of the prediction model was measured using receiver operating characteristic (ROC) analysis with "ROCR" package of R software. Calibration curves were plotted using the R software "rms" package to evaluate the calibration of the nomogram. To further estimate the clinical usefulness of the nomogram, decision curve analysis was conducted using the "rmda" package of R software. Net benefit is a weighted measure between true positives and false positives depending on the threshold probability and is a crucial component of decision curve analysis. In the decision curve analysis, the maximum net benefit is acquired via identifying all patients with echocardiography LVH. Therefore, this net benefit is equivalent to the overall prevalence of LVH in the training set. The line corresponding to the extreme assumption that all patients with LVH can be drawn (all patients were classified with LVH, traditionally called "treat all"). Likewise, the minimum net benefit is obtained by assuming that no patient with LVH and is zero (no patient was classified with LVH, traditionally called "treat none"). In order to be clinically useful, a nomogram should have a higher net benefit than the two extreme cases.²⁷ Internal validation was performed by subjecting the nomogram to bootstrapping with 1000 resamples to obtain a relatively corrected C-index.²⁸ $P < .05$ for both sides was considered significant.

3 | RESULTS

3.1 | Clinical characteristics

Overall, 832 hypertensive patients were enrolled in this study, 550 males (66.11%) and 282 females (33.89%), with an average age of 61.44 ± 12.00 years (range 19-89 years). The clinical characteristics of all patients are summarized in Table 1. All patients were categorized into non-LVH group and LVH group based on the echocardiographic results. The overall prevalence of LVH was 31.97%. Compared with the non-LVH group, patients in the LVH group had higher average age, systolic blood pressure, and glycosylated hemoglobin, lower eGFR, and uric acid levels ($P < .05$). In addition, higher proportion of female, diabetes, long duration of hypertension history (≥ 10 years), and antihypertensive treatment were observed in the LVH group relative to the non-LVH group ($P < .05$). There were no significant differences in smoking, family history of hypertension, antihyperglycemic treatment, lipid-lowering therapy, BMI, diastolic blood pressure, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and UACR between the two groups.

3.2 | Variable selection

Of the demographic and clinical variables, namely gender, smoking habit, family history of hypertension, duration of hypertension, diabetes, antihypertensive treatment, antihyperglycemic treatment, lipid-lowering therapy, age, BMI, systolic blood pressure, diastolic blood pressure, uric acid, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, eGFR, glycosylated hemoglobin, and UACR were included in the LASSO regression. After LASSO regression selection, 20 variables were reduced to 7 variables with nonzero coefficients (Figure 1). These variables included gender, age, BMI, duration of hypertension, systolic blood pressure, eGFR, and glycosylated hemoglobin.

3.3 | Development of an individualized prediction model

After that, these selected variables were together subjected to multivariate logistic regression analysis. Among them, 5 variables that were independently risk factors for LVH and were used to construct the nomogram. These variables included female gender (OR = 3.405, 95% CI: 2.447-4.740, $P < .001$), duration of hypertension (≥ 10 years: OR = 1.546, 95% CI: 1.044-2.289, $P = .030$), age, per 1 year increase (OR = 1.022, 95% CI: 1.006-1.039, $P = .008$), BMI, per 1 kg/m² increase (OR = 1.061, 95% CI: 1.006-1.118, $P = .028$), and systolic blood pressure, per 1 mmHg increase (OR = 1.018, 95% CI: 1.009-1.028, $P < .001$) (Table 2).

TABLE 1 Comparison of clinical characteristics of hypertensives with and without left ventricular hypertrophy

Variables	Overall (n = 832)	Non-LVH patients (n = 566)	LVH patients (n = 266)	P value
Gender, n (%)				<.001
Male	550 (66.11%)	423 (74.73%)	127 (47.74%)	
Female	282 (33.89%)	143 (25.27%)	139 (52.26%)	
Smoking, n (%)				.214
No	570 (68.51%)	380 (67.14%)	190 (71.43%)	
Yes	262 (31.49%)	186 (32.86%)	76 (28.57%)	
Family history of hypertension, n (%)				.748
No	404 (48.56%)	277 (48.94%)	127 (47.74%)	
Yes	428 (51.44%)	289 (51.06%)	139 (52.26%)	
Duration of hypertension, n (%)				<.001
<5 years	303 (36.42%)	230 (40.64%)	73 (27.44%)	
≥5, but < 10 years	177 (21.27%)	125 (22.08%)	52 (19.55%)	
≥10 years	352 (42.31%)	211 (37.28%)	141 (53.01%)	
Diabetes, n (%)				.033
No	522 (62.74%)	369 (65.19%)	153 (57.52%)	
Yes	310 (37.26%)	197 (34.81%)	113 (42.48%)	
Antihypertensive treatment, n (%)				.017
No	282 (33.89%)	207 (36.57%)	75 (28.20%)	
Yes	550 (66.11%)	359 (63.43%)	191 (71.80%)	
Antihyperglycemic treatment, n (%)				.270
No	663 (79.69%)	457 (80.74%)	206 (77.44%)	
Yes	169 (20.31%)	109 (19.26%)	60 (22.56%)	
Lipid-lowering therapy, n (%)				.857
No	701 (84.25%)	476 (84.10%)	225 (84.59%)	
Yes	131 (15.75%)	90 (15.90%)	41 (15.41%)	
Age, years	61.44 ± 12.00	59.73 ± 12.03	65.09 ± 11.10	<.001
BMI, kg/m ²	25.29 ± 3.04	25.19 ± 2.92	25.49 ± 3.28	.189
Systolic blood pressure, mmHg	137.57 ± 17.46	135.31 ± 16.24	142.37 ± 18.97	<.001
Diastolic blood pressure, mmHg	79.03 ± 11.15	79.46 ± 10.60	78.11 ± 12.22	.104
Uric acid, mmol/L	381.12 ± 97.94	385.84 ± 93.85	371.08 ± 105.60	.043
Total cholesterol, mmol/L	4.53 ± 1.09	4.57 ± 1.08	4.46 ± 1.12	.178
Triglyceride, mmol/L	1.33 (0.98-1.83)	1.34 (0.98-1.87)	1.32 (0.98-1.74)	.110
HDL cholesterol, mmol/L	1.19 ± 0.34	1.20 ± 0.36	1.18 ± 0.30	.425
LDL cholesterol, mmol/L	2.83 ± 1.00	2.86 ± 0.99	2.76 ± 1.01	.189
eGFR, ml/min	103.38 ± 27.42	105.63 ± 26.32	98.59 ± 29.11	.001
Glycosylated hemoglobin, %	6.24 ± 1.25	6.14 ± 1.17	6.46 ± 1.38	.001
UACR, mg/g	8.04 (4.72-17.98)	7.08 (4.49-15.83)	10.92 (5.79-26.12)	.954
EDD, cm	4.78 ± 0.52	4.71 ± 0.48	4.95 ± 0.55	<.001
SWT, cm	1.01 ± 0.11	1.00 ± 0.07	1.03 ± 0.16	.002
PWT, cm	1.00 ± 0.07	1.00 ± 0.06	1.01 ± 0.09	.032
LVM, g	176.38 ± 43.57	160.73 ± 31.89	209.67 ± 46.37	<.001
LVMI, g/m ²	101.99 ± 22.53	91.49 ± 13.77	124.33 ± 21.26	<.001

Note: Data are expressed as means ± SD or median (25th–75th).

Abbreviation: BMI, body mass index; EDD, end-diastolic dimension; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; PWT, posterior wall thickness; SWT, septal wall thickness; UACR, urinary albumin-to-creatinine ratio.

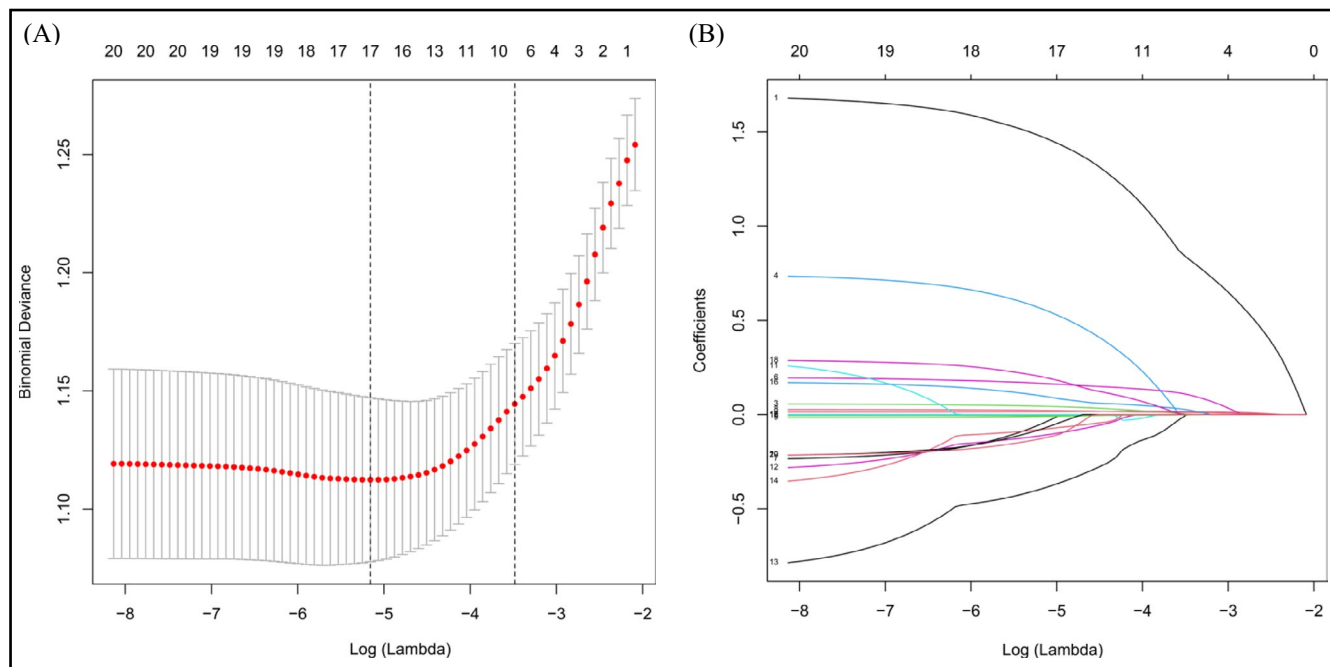


FIGURE 1 Variable selection using the LASSO binary logistic regression model. A, Optimization parameters (lambda) of the LASSO model were obtained via 10-fold cross-validation. The partial likelihood deviance (binomial deviance) curve was plotted versus log (lambda). Dotted vertical lines were drawn at the optimal values based on the minimum criteria and the one standard error of the minimum criteria. Seven variables with nonzero coefficients were selected based on the one standard error of the minimum criteria. B, The LASSO coefficient profiles of the 20 variables. The coefficient profile plot was produced against the log (lambda) sequence. Abbreviation: LASSO, the least absolute shrinkage and selection operator

TABLE 2 Multivariate analysis of risk factors for LVH

Variables	β	OR (95% CI)	P value
Gender			
Male	Reference	Reference	
Female	1.225	3.405 (2.447-4.740)	<.001
Duration of hypertension			
<5 years	Reference	Reference	
≥ 5 , but < 10 years	0.275	1.317 (0.840-2.065)	.230
≥ 10 years	0.435	1.546 (1.044-2.289)	.030
Age ^a	0.022	1.022 (1.006-1.039)	.008
BMI ^b	0.059	1.061 (1.006-1.118)	.028
Systolic blood pressure ^c	0.018	1.018 (1.009-1.028)	<.001
eGFR ^d	-0.007	0.993 (0.987-1.000)	.057
Glycosylated hemoglobin ^e	0.107	1.113 (0.981-1.263)	.096

Abbreviation: BMI, body mass index; eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval.

^aOR is per each 1-year increment in age.

^bOR is per each 1-kg/m² increment in BMI.

^cOR is per each 1-mmHg increment in systolic blood pressure.

^dOR is per each 1-ml/min increment in eGFR.

^eOR is per each 1-% increment in glycosylated hemoglobin.

Based on the results from the multivariate logistic regression analysis, a nomogram was constructed for predicting the probability of LVH (Figure 2A). The nomogram was composed of 8 axis and axis 2-6 denoting each variable of the regression model. A certain point was assigned to each subtype of these variables by drawing a vertical line up to the "Points" axis, then sum the points from all 5 variables of risk factors, and locate this number on the "Total Points" axis. The corresponding predicted probability of LVH could be found on the bottom axis. For instance, using this nomogram, a female patient with hypertension of age 50 years, a BMI of 25.52 kg/m², a systolic blood pressure of 152 mmHg, and a duration of hypertension diagnosis < 5 years has the estimated probability of LVH of 42.75% (Figure 2B).

3.4 | Performance assessment of the nomogram

The performance of the nomogram was evaluated using the ROC curve and the calibration curve. This nomogram achieved moderate discrimination, with the area under the ROC curve (AUC) of 0.724 (95% CI: 0.687-0.761) (Figure 3A). The calibration curve also demonstrated an accordant agreement between actual observation and prediction by the nomogram (Figure 3B). A bias-corrected estimate of the calibration curve (mean absolute error = 0.008) was obtained using the bootstrap method (1000 repetitions).

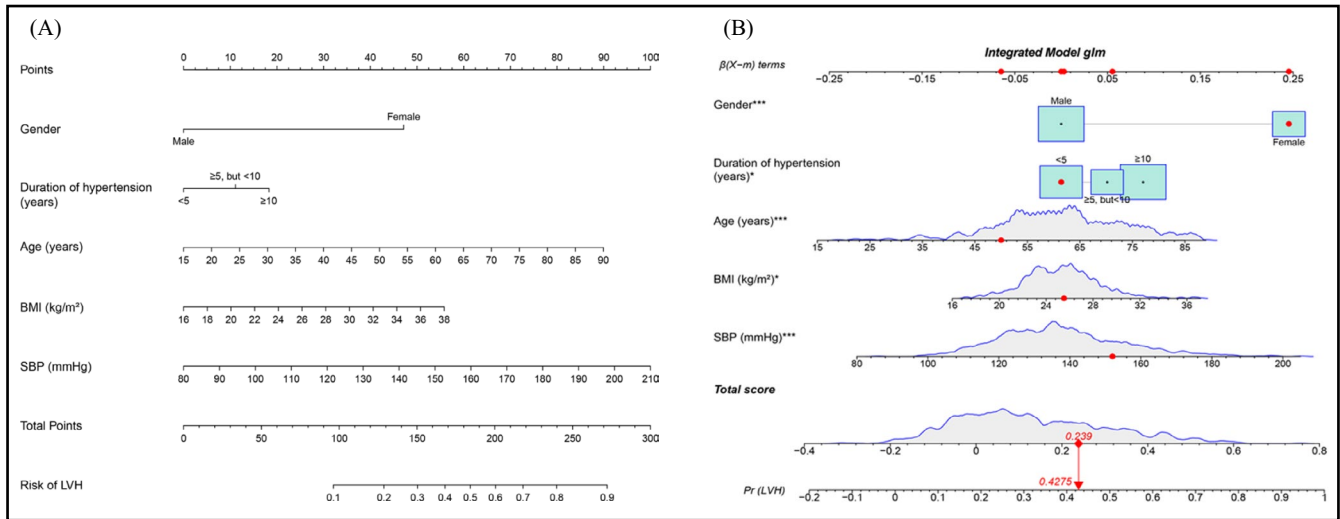


FIGURE 2 Development of the risk nomogram. A, The LVH risk nomogram was developed using the predictors, including gender, duration of hypertension, age, BMI, and SBP. B, Dynamic nomogram used as an example. Abbreviation: BMI, body mass index; LVH, left ventricular hypertrophy; SBP, systolic blood pressure

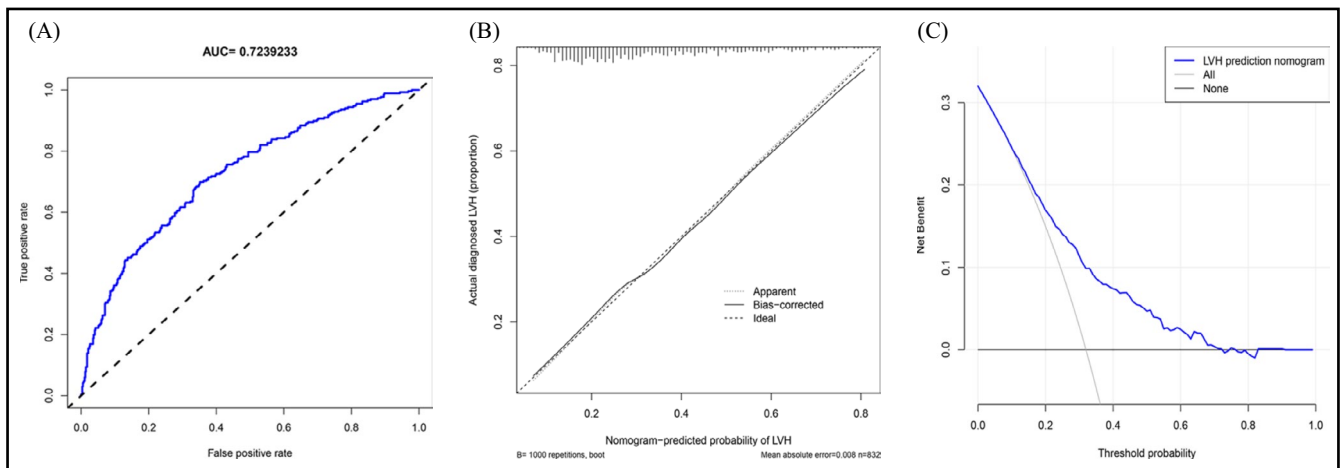


FIGURE 3 Evaluation of the nomogram. A, ROC curve of the model showing the prediction power for LVH. The AUC was 0.724 (95% CI: 0.687-0.761). B, The calibration curves of the prediction model for LVH. The diagonal dotted line represents the ideal curve, the solid line represents the bias-correction curve, and the dashed line represents the apparent curve. C, Decision curve analysis of the LVH risk nomogram. The y-axis measures the net benefit. The gray line represents the assumption that all patients had LVH. The black line represents the assumption that no patients had LVH. The blue line represents the risk nomogram. Abbreviation: AUC, the area under the ROC curve; LVH, left ventricular hypertrophy

3.5 | Clinical application of the nomogram

The potential clinical utility was evaluated using the decision curve analysis. Between the threshold probability of 5% and 72%, using the nomogram to predict the probability of LVH added more benefit than the “treat none” or “treat all” strategies (Figure 3C).

3.6 | Model validation

The internal validation was performed using the bootstrap method with 1000 resamples, the C-index, bias-corrected Somers’ D_{xy}

rank correlation (D_{xy}), and R-squared index (R^2) in the testing set were 0.715, 0.430, and 0.172; and in the training set, they were 0.724, 0.449, and 0.188 (Table 3). These data suggested that the predictive abilities for the training set and testing set were highly consistent.

4 | DISCUSSION

In this study, a nomogram was constructed to assess the risk of LVH in Chinese hypertensives based on a clinical analysis. Five easily obtained clinical indexes were included in the prediction model. This

TABLE 3 Internal validation of the prediction model

Items	Training set	Testing set
C-index	0.724	0.715
D_{xy}	0.449	0.430
R^2	0.188	0.172

Abbreviation: D_{xy} , bias-corrected Somers' D_{xy} rank correlation; R^2 , R-squared index.

nomogram constitutes an easily used tool for individualized risk assessment and clinical decision making.

A nomogram is a straightforward graphical tool and allows clinicians to estimate the impact of multiple factors on the probability of clinical outcomes without the need for complex Equation 29. Hence, this tool could be easily used even with clinicians lacking statistical knowledge. At present, nomograms have extensively been used in daily clinical practice as prognostic tools in a variety of cancers.³⁰ In this study, a nomogram based on five easily accessible items (gender, duration of hypertension, age, BMI, and systolic blood pressure) for estimating the probability of LVH in Chinese hypertensives was developed. This nomogram could help clinicians to identify the high-risk individuals and take appropriate intervention accordingly without sophisticated medicine examination. The performance of this nomogram was assessed using the ROC curve and calibration curve, which demonstrated that the model had favorable discrimination and calibration abilities. The decision curve analysis also confirmed a potential clinical benefit of using this nomogram. The internal validation showed a good consistency between the training set and the testing set. This implies that our nomogram could potentially be widely used in the clinical setting.

It is known that there are ethnic differences in the prevalence of LVH.^{10,11} A previous study reported a significantly higher prevalence of LVH among blacks compared with whites.¹⁰ It has also been documented that Caribbean Hispanics have higher prevalence of LVH and left ventricular remodeling, compared with non-Hispanic whites.¹¹ Moreover, the association between LVH and cardiovascular events may also differ by ethnic background.^{12,13} Havranek et al¹² reported that the relationship between LVH and cardiovascular mortality is significantly stronger among African Americans compared with Whites. Similarly, Akintoye et al¹³ indicated that LVH is a stronger predictor of cardiovascular events in Chinese and Hispanics relative to non-Hispanic Whites. Therefore, compared with other races, Chinese and Hispanics could benefit more from risk stratification of LVH. To date, only a few LVH risk prediction models have been developed. Most of the participants in the previous study were derived from white patients. Our group reported the prognostic significance of various specific electrocardiographic changes in hypertensive patients with LVH.³¹ To the best of our knowledge, this is the first study to develop a prediction tool for Chinese hypertensives to evaluate the probability of LVH.

In the present study, variables selected by LASSO regression were together subjected to multivariate logistic regression analysis

and those that were statistically significant used to build the nomogram. Female gender was identified as an independent risk factor for LVH in this study. To date, there have been controversies regarding the association between gender and LVH. Recently, a study reported that female patients with hypertension were shown to be more vulnerable to developing LVH compared with the males,³² and the condition of combined LVH in hypertension offset the gender-specific benefits in cardiovascular risk.³³ Previously, our research team had reported that gender may have impact on the LVH.³⁴ Data from another study conducted in a European country, however, suggested that the male gender is an independent risk factor for LVH.³⁵ These inconsistencies could be attributed to the differences in study populations and methodologies (eg, measurement methods, diagnostic criteria). In the present study, most of the females were postmenopausal in the condition of estrogen deficiency, lacking of the protection of the cardiovascular system. Furthermore, the use of gender-specific cutoffs was also likely to overestimate the prevalence of LVH in females. Either of these situations explains why female hypertensives are at a higher risk of LVH. Similar to the previous study, the duration of hypertension was shown as an independent risk factor for LVH in our study. As reported by Nardi et al,⁷ the duration of hypertension is able to independently predict the presence of LVH. Furthermore, increasing age was closely related to the increase in LVMI, consistent with some previous studies.^{6,35,36} It has been reported that LV mass increases gradually with aging in patients both with and without hypertension.³⁷ Our study suggested that obesity is also an independent risk factor for LVH congruent with the existing evidence.^{6,8,36} Multiple mechanisms including insulin resistance,³⁸ cardiac ectopic fat deposition,³⁹ and obesity-related increased blood volume⁴⁰ potentially account for this association. A positive association between systolic blood pressure and the risk of LVH was observed in this study. It is generally accepted that systolic blood pressure is the most important driver for ventricular hypertrophy and concentric cardiac-remodeling.⁴¹

In order to evaluate the clinical utility of this nomogram, we performed decision curve analysis. This novel approach provides insights into the clinical outcomes based on the threshold probability, from which the net benefit can be drawn. The net benefit was calculated as the proportion of true positives less the proportion of false positives, and by weighing the relative hazards of forgoing treatment and the negative consequences of an unnecessary treatment.²⁷ The decision curve analysis demonstrated that the use of this nomogram to predict the probability of LVH added more benefit compared with the "treat none" or "treat all" strategies in the range of thresholds from 5% to 72%.

A well-performed LVH risk prediction tool could be beneficial for clinical decision making. The development of LVH is undoubtedly associated with a greater risk of adverse cardiovascular events and death.⁴ Therefore, screening and early diagnosis of LVH is essential to reduce the risk of adverse cardiovascular events. In this study, a nomogram based on five easily accessible parameters was developed. Efforts should be directed at implementing preventive

interventions in high-risk cohorts that target the modifiable factors, such as BMI and systolic blood pressure, to reduce the risk of LVH. Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that intensive antihypertensive therapy is able to prevent the development of LVH.⁴² Furthermore, it has been reported that the combination of weight loss and antihypertensive therapy strategy could contribute to reduction of left ventricular mass.⁴⁰ Regarding nonmodifiable factors, such as gender, age, and duration of hypertension, it is also helpful for the general public to be fully aware of the LVH risk. The nomogram developed in this study is able to identify high-risk patients using only five routine clinical parameters, which could be an attractive option for the general population, primary health clinics, or people with low socioeconomic status.

In the actual clinical setting, the electrocardiogram (ECG) is a common screening tool for LVH due to its low cost and wide availability and is recommended as a routine examination for hypertensive patients in the Chinese hypertension guidelines.²³ Several ECG criteria, including Sokolow-Lyon voltage, RavL voltage, Cornell voltage, and Cornell product, can be used to assess LVH.²² However, it is generally known that the sensitivity of ECG to detect LVH is rather low, particularly in the Chinese and other eastern Asian populations.⁴³ In contrast, echocardiography has a high sensitivity for detecting LVH, but limited availability and high skill requirement. In fact, prescribing echocardiography as a routine examination in hypertensive patients is an issue opens for debate. According to the 2018 ESC/ESH hypertension guidelines, echocardiography is performed as a second-level examination technique for LVH, to be applied only when specific information on heart structure and function will influence treatment options.²² Moreover, the 2017 ACC/AHA hypertension guidelines explicitly indicate that the use of echocardiography for the assessment of LVH is not routinely recommended due to a lack of cost-effectiveness evidence.⁴⁴ As a result, a comprehensive analysis of ECG and this nomogram could serve as a prescreening method before employment of echocardiography for the assessment of LVH. If implemented properly, this strategy might improve LVH screen in hypertensive patients.

In contrast to previous studies, our study has several characteristics. Firstly, patients spread across a wide age group and severities of hypertension were included in this study. Hence, our results could cover and be used generally to evaluate the situation of LVH in Chinese hypertensives. Secondly, a novel statistical method was used in the process of model construction. In order to simplify the model and prevent overfitting as much as possible, the LASSO regression and multivariate logistic regression analysis were utilized to shrink candidate variables and construct the prediction model. Thirdly, the complicated predictive formula was converted to a concise nomogram to be easily used in clinical practice. Fourthly, the indicators included in this nomogram are conventional clinical indices, which do not require any other additional expense. Finally, the clinical utility of this nomogram was evaluated through decision curve analysis.

However, our study has some limitations. Firstly, this paper was a cross-sectional observational study, although verified by decision

curve analysis, as many other retrospective observational studies, assumptions regarding causal relationships are limited. As a result, our results should be further validated by prospective studies. Secondly, the number of cases in our study was relatively small. Therefore, some true associations may have been neglected due to a lack of statistical power. Finally, it was a single-center study. The patients were mostly selected from Fujian province, which may limit generalizability. Although the bootstrap technique was applied for internal validation, external validation using a prospective multi-center study should also be conducted in the future.

In summary, our results highlight some key risk factors of LVH, including gender, duration of hypertension, age, BMI, and systolic blood pressure, among Chinese hypertensives. A user-friendly nomogram was developed based on the risk factors identified in the present study. We believe that the utilization of this nomogram will help to identify individuals at high risk of LVH, help clinical decision making, and thus prevent adverse cardiovascular events. Nevertheless, further external validation data are required to ascertain the stability and applicability of this nomogram.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Chaoyi Ye contributed to the conception and design of the work; analysis and interpretation of data for the work; and drafting the work. Tingjun Wang contributed to the design of the work and critical revision for important intellectual content. Jin Gong and Xiaoqi Cai contributed to the acquisition and analysis of data and critical revision for important intellectual content. Guili Lian, Li Luo, and Huajun Wang contributed to the acquisition of data and critical revision for important intellectual content. Liangdi Xie contributed to critical revision of the manuscript and final version approval.

DATA AVAILABILITY STATEMENT

The data of this study are available from the corresponding author on reasonable request.

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