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One-Year Risk Prediction of Elevated Serum Uric Acid Levels in Older Adults: A Longitudinal Cohort Study

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Objective: To develop and externally validate a nomogram to predict elevated serum uric acid (SUA) levels in older adults.

Study Design: This is a longitudinal Chinese cohort study.

Methods: A cohort of 2788 older adults was established at Huadong Hospital, followed-up for at least one year, and screened for risk factors for elevated SUA levels. A logistic regression model was built to predict elevated SUA, and its performance was validated.

Results: The risk prediction model showed good discrimination ability in both the development cohort (area under the curve (AUC) = 0.82; 95% confidence interval (CI) =0.79~0.86) and the external validation cohort (AUC=0.76; 95% CI=0.70~0.82). The model was adequately calibrated, and the predictions correlated with the observed outcome ($\chi^2 = 6.36$, $P = 0.607$). Men were more prone to elevated SUA levels than women were, and a baseline SUA level ≥360 μmol/L was a common risk factor for both males and females. Proteinuria status was an additional risk factor for males, whereas a baseline estimated glomerular filtration rate (eGFR)<60 mL/min·1.73 m^2 and diabetes status were additional risk factors for females.

Conclusion: The externally validated nomogram, which is predictive of elevated SUA in older adults, might aid in the detection of individual diseases, the development of preventive interventions and clinical decision-making.

Keywords: elevated serum uric acid, prediction nomogram, risk factor

Introduction

Hyperuricemia (HUA) comprises a heterogeneous group of disorders caused by impaired purine metabolism and/or decreased uric acid (UA) excretion.[1] In addition to triggering gout, elevated serum UA (SUA) is an independent risk factor for the development of chronic kidney disease (CKD), hypertension, cardiovascular disease, dyslipidemia and impaired glucose metabolism.[2–7] Additionally, patients with asymptomatic HUA may have urate deposits in joints and even bone erosion, suggesting that asymptomatic HUA-related gout is a continuous pathological process.[8] Although this phenomenon has not been confirmed in all populations, studies have confirmed that high SUA levels are significantly associated with the presence of numerous cardiovascular risk factors and the risk of developing cardiovascular disease, even in elderly individuals.[9–11] For example, a cross-sectional study from China showed that higher SUA levels, even within the normal range, are positively associated with metabolic syndrome in older adults in Chinese communities, and the correlation is stronger in women than in men.[12] Moreover, the prevalence of HUA also increases significantly with age.[13] A 2021 meta-analysis including 2,277,712 participants revealed that the prevalence of HUA has increased to 16.4% (20.4% in men and 9.8% in women) in China. Moreover, the prevalence of HUA also increases significantly with age, with a prevalence of 18.8% to 22.3% in people older than 60 years of age.[14] From 2020 to 2050, China's population

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aged ≥65 years is estimated to more than double from 172 million (12·0%) to 366 million (26·0%).[15] With the rapid aging of the population, there is an urgent need for the early identification of risk factors associated with the development of HUA to reduce the risk of developing HUA through a variety of measures that are relevant to the well-being of elderly people, which will further benefit global sustainable development and healthy aging.[16]

Fewer studies on HUA risk factors and prediction models in the elderly population have been reported. The metabolic profile of elderly individuals is different from that of young individuals and should be treated differently. The Framingham Heart Study revealed that SUA levels remained stable in males after puberty, but in females, SUA levels gradually increased after middle age.[17] Most of the current HUA risk prediction models are based on the general population. Gao et al[18] constructed a random forest prediction model for health checkups. Cao et al[19] established a simple HUA Cox proportional risk model based on a Chinese urban-dwelling population, which had good clinical discrimination between males and females [C-index: 0.783 (95% confidence interval (CI): 0.779–0.786) vs 0.784 (95% CI: 0.778–0.789)]. However, no external validation has been performed to test the model's ability to generalize to new environments. In addition, machine learning-based risk prediction models, such as artificial neural networks, have been used for HUA prediction.[20,21] Predictive models are built to better serve the clinic, so they need to be characterized by strong predictive ability, visualization, and easy operation. Nomograms provide tools for the visual representation of prediction models. The establishment of HUA risk prediction can help physicians develop earlier and more effective intervention strategies for high-risk patients and reduce the occurrence of complications such as gout.

The aim of this study was to explore the risk factors for the development of HUA in elderly individuals. We established a specific cohort of elderly people, derived risk factors specific to abnormally elevated SUA in elderly individuals, and developed an internally validated predictive model for predicting the occurrence of elevated SUA levels at one year. The model showed good sensitivity and specificity, and its use will help clinicians accurately predict associated risks and take appropriate measures to reduce the incidence of abnormally elevated SUA in the elderly population and alleviate the health problems caused by aging.

Methods

Study Design and Participants

A longitudinal cohort study was conducted. Participants' baseline information was collected, and each participant was followed up for a period of one year after their enrollment between 2015 and 2021. We tested SUA levels the next year and defined participants whose SUA level was >420 μmol/L as those with elevated SUA.[22–24]

We used the events per variable (EPV) criteria to estimate the minimal sample size needed.[25] In our study, we set the EPV to 10 and the number of candidate predictors to 12; thus, we needed 120 positive events. Furthermore, the estimated proportion of positive events was approximately 7%~15% in our study population, so we needed a minimum sample size of 1715.

We used a cluster random sampling method to recruit retirees from 25 public institutions in Shanghai as the research participants. Individuals who met the inclusion and exclusion criteria were included in the cohort. The inclusion criteria were as follows: 1) aged 60 years or older, 2) had a baseline SUA level <420 μmol/L, and 3) voluntarily participated in the study, abided by the study rules, understood and complied with the follow-up plan. Pregnant women and patients with severe renal insufficiency (estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2); severe hepatic insufficiency (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 120 U/L); or the presence of acute infections, malignant neoplasms, or psychiatric disorders were excluded. A total of 3089 participants were included in the cohort, and 2788 participants were followed up for one year (the one-year loss to follow-up rate was 9.7%). There were no significant differences in baseline characteristics between the population lost to follow-up and the study population (shown in Supplementary Table S1). The 2788 participants were divided into a development cohort of 2287 subjects, which was built between 2015 and 2019 (26, 70, 570, 227, and 1394 subjects enrolled in the above years, respectively), and an external validation cohort of 501 subjects (365 subjects enrolled in 2020 and 136 subjects enrolled in 2021) according to the year the participant was enrolled in the cohort; the flowchart of study participant enrollment is shown in Figure 1.

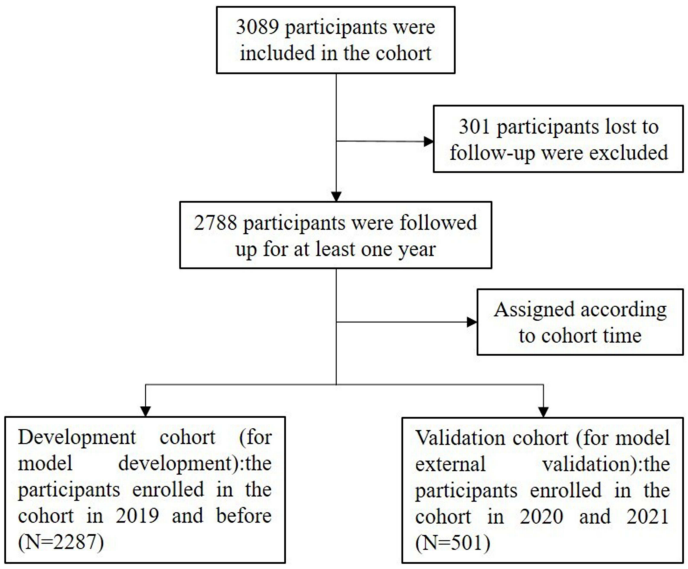

Figure 1 Flowchart of study participant enrollment in the development and validation cohorts. The 2788 participants who completed the 1-year follow-up were taken as the research participants of this study and assigned to two cohorts, a development cohort and a validation cohort, according to the time of their enrollment.

Data Collection

Data for this study were collected through participant interviews, which included demographic data such as age, sex, and history of underlying diseases such as hypertension, diabetes, and fatty liver. The height, weight and blood pressure of the subjects were measured as part of the physical examination. The height was measured with the participants standing upright and without a hat or shoes (the value obtained was accurate to 0.01 m). The weight was measured without shoes and with an empty bladder (the value obtained was accurate to 0.1 kg). Body mass index (BMI) was calculated by dividing the current weight (kg) by the square of the height (m^2). Blood pressure was measured by trained nurses and clinical technicians. Before the blood pressure measurements were taken, the subjects were asked to abstain from drinking alcohol, smoking, drinking tea or coffee and performing vigorous exercise, and they rested for at least 5 min. Their blood pressure was measured twice in succession on the right upper arm with an appropriately sized cuff attached to a HEM-907 (OMRON Co. Ltd., Kyoto, Japan), an oscillometric automated digital sphygmomanometer.[26] In this study, the mean value was used as the blood pressure data, and a blood pressure of 140/90 mmHg or higher was considered to indicate the presence of hypertension. After 12 hours of fasting, venous blood was collected for measurement. Blood glucose, cholesterol (CHOL), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum creatinine (sCr), ALT, AST, calcium (Ca), phosphorus (P), and SUA levels were measured via the photometric and ion-selective electrode (ISE) methods (Hitachi Model 7600 analyzer, Hitachi, Tokyo, Japan). The white blood cell (WBC) count, red blood cell (RBC) count, platelet (PLT) count, eosinophils, basophils, lymphocytes, monocytes, hemoglobin (Hb) and other routine blood indicators were measured via flow cytometry and the electrical impedance method (LH 780 hematology Analyzer, Beckman Coulter, Inc., California, America). In addition, urine specific gravity, urine pH, urinary protein, urinary ketone bodies, urinary bilirubin, urinary RBCs, urinary WBCs, urinary epithelial cells and other routine urine indicators were measured via dry chemistry combined with the optical detection method (Roche Cobas u 411 urine analyzer, Roche, Basel, Switzerland). In addition, we also considered and analyzed the impact of the eGFR on SUA levels. The eGFR was calculated via the CKD Epidemiology Collaboration (CKD-EPI) formula: 141×min (SCr/k,1)^a×max(SCr/k,1)^(−1.209) × (0.993^ age) ×b (k=0.7; a=−0.329; b=1.018 for females; k=0.9; a=−0.411; b=1 for males).[27]

Outcome

The outcome event was the occurrence of elevated SUA concentrations (SUA >420 μmol/L) at the one-year follow-up. Statistical analysts analyzed the data without knowing information about the grouping of predictor variables and outcomes to ensure objectivity in data analysis.

Statistical Analysis

Statistical analysis was performed via R (version 4.0.1, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were tested by the Kolmogorov–Smirnov test for normality and are presented as the mean and standard deviation (SD) if normally distributed and as the median and interquartile range (IQR) if not normally distributed. Categorical variables are presented as frequencies and rates. Comparisons of continuous variables were performed with the *t* test or Wilcoxon test according to their normality. The chi-square test or Fisher's exact test was used to compare categorical variables. Stratified analysis for sex was used to compare risk factors for different sexes. All the statistical tests were 2-tailed, and $P<0.05$ was considered to indicate statistical significance. We used the missForest algorithm to fill in the variables if the proportion of missing data was less than 20% (the missing rate of BMI was 1.5%).[28] We used the EPV criteria to estimate the sample size with the expectation of including 10 predictive factors (EPV=12). The percentage of positive events (elevated SUA levels) in the previous experiment was approximately 8%; therefore, the necessary sample size was estimated to be 10*12/0.08=1500.

Prediction Model Construction and Validation

Univariate logistic regression (LR) was used to screen possibly relevant factors of "elevated SUA", and multivariate LR was applied to estimate the odds ratios (ORs) and their 95% CIs or p values of the independent risk factors in the development cohort; the results are displayed in the form of forest plots. The prediction accuracy of the LR model was evaluated via two methods. First, the discriminatory ability of the models was assessed by the area under the receiver operating characteristic curve (AUC) and its 95% CI; the utility of the models was assessed by computing the sensitivity and specificity in the development and validation cohorts. Second, model calibration was evaluated with a calibration curve (predicting the probability of developing elevated SUA levels at the one-year follow-up versus the observed probability) and the Hosmer–Lemeshow test.

Explanation and Application of the Prediction Model

A nomogram was generated from the model to indicate the weight of each meaningful variable on the outcome event and to determine the individual risk scores and probability of the occurrence of the outcome event according to the values of the relevant variables for each individual.

Ethical Approval

This study was approved by the Ethics Committee of Huadong Hospital, Fudan University (Approval No. 20200070). All procedures were conducted in accordance with the Declaration of Helsinki. This was an observational study, and no intervention measures were implemented for the participants; therefore, informed consent was exempt.

Results

Participant Characteristics at Baseline

A total of 2788 participants were included in this study, consisting of 2556 individuals with normal SUA levels and 232 with elevated SUA levels. Among the participants, 2087 (74.9%) had baseline SUA levels below 360 μmol/L. Among the elderly population, the incidence of elevated SUA levels after one year was 6.5%, with elderly males being more susceptible to this increase. Significant differences between the two groups ($P<0.05$) were observed in terms of age, BMI, lipid metabolism parameters (HDL, CHOL, TGs), medical history (hypertension, diabetes, fatty liver disease), kidney function (eGFR, SUA), and proteinuria. A total of 2287 participants were randomly assigned to the training set, and 501 were assigned to the validation set. Significant differences ($P<0.05$) in basic characteristics, such as sex, age, lipid metabolism (HDL, TGs), medical history (fatty liver disease, kidney stones), urine pH, and kidney function (SUA), were noted between these two groups (Table 1).

Table 1 Baseline Characteristics of the Study Participants

Variables	Total (n=2788)	Non-Elevated SUA (n=2556)	Elevated SUA (n=232)	*P value*	Development Cohort (n=2287)	Validation Cohort (n=501)	*P value*
Male[a]	1171(42.00)	1010(39.51)	161(69.40)	<0.001	925(40.45)	246(49.10)	<0.001
Age (years)[a]				0.039			<0.001
60–69	1633(58.57)	1513(59.19)	120(51.72)		1301(56.89)	332(66.27)	
70–79	877(31.46)	797(31.18)	80(34.48)		759(33.19)	118(23.55)	
≥80	278(9.97)	246(9.62)	32(13.79)		227(9.93)	51(10.18)	
BMI (kg/m^2)[a]				<0.001			0.349
<18.5	119(4.27)	111(4.34)	8(3.45)		100(4.37)	19(3.79)	
18.5–23.9	1270(45.55)	1191(46.60)	79(34.05)		1024(44.77)	246(49.1)	
24.0–27.9	1074(38.52)	971(37.99)	103(44.40)		895(39.13)	179(35.73)	
>27.9	325(11.66)	283(11.07)	42(18.10)		268(11.72)	57(11.38)	
HDL (mmol/L)[b]	1.54(1.3,1.83)	1.56(1.32,1.84)	1.36(1.18,1.62)	<0.001	1.54(1.31,1.83)	1.51(1.28,1.78)	0.023*
LDL (mmol/L)[b]	3.01(2.44,3.60)	3.01(2.44,3.60)	2.99(2.30,3.63)	0.317	2.98(2.43,3.56)	3.14(2.51,3.78)	<0.001
Cholesterol (mmol/L)[b]	5.1(4.40,5.75)	5.11(4.42,5.76)	4.965(4.18,5.66)	0.025	5.1(4.4,5.76)	5.08(4.4,5.72)	0.649
Triglycerides (mmol/L)[b]	1.40(1.09,1.90)	1.40(1.00,1.90)	1.7(1.30,2.20)	<0.001	1.4(1,1.9)	1.47(1.1,2.08)	0.008*
Disease history							
Hypertension (Yes)[a]	346(12.41)	306(11.97)	40(17.24)	0.020	281(12.29)	65(12.97)	0.673
Diabetes (Yes)[a]	128(4.59)	111(4.34)	17(7.33)	0.038	97(4.24)	31(6.19)	0.059
Fatty liver[a]				0.006			0.006*
No	1383(49.61)	1288(50.39)	95(40.95)		1165(50.94)	218(43.51)	
Trendy	560(20.09)	512(20.03)	48(20.69)		440(19.24)	120(23.95)	
Mild	311(11.15)	285(11.15)	26(11.21)		243(10.63)	68(13.57)	
Moderate	534(19.15)	471(18.43)	63(27.16)		439(19.2)	95(18.96)	
Kidney stone (Yes)[a]	124(4.45)	108(4.23)	16(6.90)	0.059	93(4.07)	31(6.19)	0.037*
Baseline Tests							
Proteinuria (Yes)[a]	164(5.88)	134(5.24)	30(12.93)	<0.001	126(5.51)	38(7.58)	0.074
Urine pH[a]				0.596			<0.001
<6	1538(55.16)	1409(55.13)	129(55.60)		1160(50.72)	378(75.45)	
6–7	1203(43.15)	1102(43.11)	101(43.53)		1084(47.4)	119(23.75)	
>7	47(1.69)	45(1.76)	2(0.86)		43(1.88)	4(0.8)	
eGFR (mL/min/1.73m^2)[a]				<0.001			0.342
<60	247(8.86)	194(7.59)	53(22.84)		200(8.75)	47(9.38)	
60–90	1885(67.61)	1738(68)	147(63.36)		1560(68.21)	325(64.87)	
>90	656(23.53)	624(24.41)	32(13.79)		527(23.04)	129(25.75)	
Serum uric acid (μmol/L)[a]				<0.001			0.004*
<360	2087(74.86)	2016(78.87)	71(30.60)		1737(75.95)	350(69.86)	
≥360	701(25.14)	540(21.13)	161(69.40)		550(24.05)	151(30.14)	
Primary endpoint		/	/				
1-year serum uric acid >420μmol/L[a]	232(8.32)				161(7.04)	71(14.17)	<0.001

Notes: [a] Categorical variables, expressed as n(%). [b] Continuous variable, expressed as the median (IQR).
Abbreviations: SUA, serum uric acid; eGFR, estimated glomerular filtration rate; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Risk Factor Screening and Risk Prediction Model Development

Among the 2788 patients, 232 (8.32%) had elevated SUA levels (>420 μmol/L) at the one-year follow-up. A comparison of the different baseline groups in the development cohort revealed that sex; BMI; HDL cholesterol; history of hypertension, diabetes or fatty liver; baseline SUA level; proteinuria; and the eGFR might be related to elevated SUA levels (Supplementary Table S2). Furthermore, multivariate LR revealed that males had a greater risk of elevated SUA

levels than females did (OR=1.90, 95% CI=1.28~2.85). Overall, a baseline SUA level>360 μmol/L (OR=6.70, 95% CI=4.59~9.90), a baseline eGFR<60 mL/min·1.73 m^2 (OR=3.27, 95% CI=1.67~6.52) and proteinuria status (OR=2.56, 95% CI=1.44~4.43) were risk factors for elevated SUA levels (OR=2.94, 95% CI=1.65~5.29) (Figure 2). However, there were significant differences between males and females in the development cohort; specifically, only baseline SUA levels ≥360 μmol/L were a common risk factor for both males and females in the development cohort, and the risk was much greater for males than for females (OR=8.57 [male] vs OR=4.72 [female]) when stratified analysis of different sexes was conducted. Proteinuria status was a risk factor only for males (OR=2.84, 95% CI=1.44~5.48), whereas a baseline eGFR<60 mL/min·1.73 m^2 (OR=9.40, 95% CI=3.16~29.19) and diabetes status (OR=8.07, 95% CI=2.07~27.52) were risk factors only for females (Supplementary Figure 1A and B).

Performance of the Prediction Model

From the perspective of discrimination, the LR model had good predictive performance for the 1-year probability of developing elevated SUA levels, with an AUC of 0.820 (95% CI95% CI: 0.786~0.855) in the development cohort, which was slightly greater than that in the validation cohort (0.762); the sensitivity and specificity were 0.776 and 0.788, respectively, in the development cohort, which were also slightly greater than those in the validation cohort (Figure 3). The male and female cohorts also exhibited good performance, with AUCs of 0.821 and 0.801, respectively

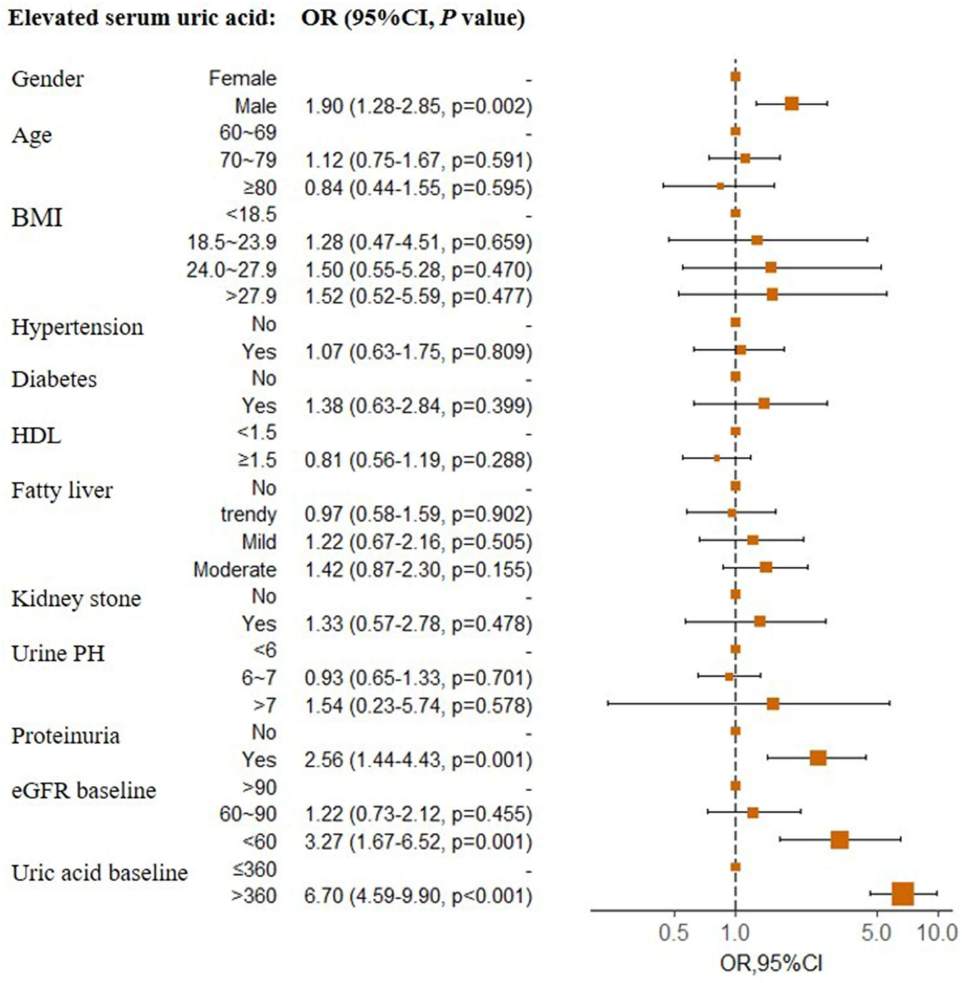

Figure 2 Forest plot of the associations between the predictors and elevated serum uric acid levels according to multivariate logistic regression analysis. The right side of the dotted line shows elevated serum uric acid levels.

Abbreviations: OR, odds ratio; BMI, body mass index; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.

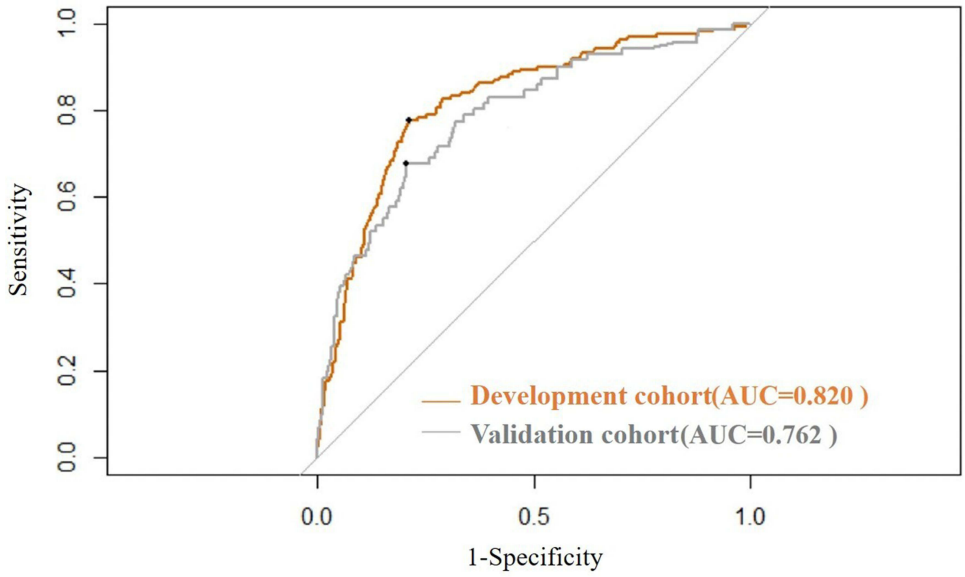

Figure 3 Receiver operating characteristic curve of the prediction performance of each algorithm in the development cohort and validation cohort.

(Supplementary Figure 2A and B). A comparison of the AUCs, sensitivities and specificities of the different models in different populations is shown in Table 2.

From the perspective of calibration, the Hosmer–Lemeshow goodness-of-fit test in both the development cohort and validation cohort demonstrated that the model was a good fit (χ^2=6.41, P=0.601 [development cohort]; χ^2= 6.36, P= 0.607 [validation cohort]), and the results are visually displayed in the calibration plot. As shown in Figure 4A and B, the calibration curves of the model in the development cohort and validation cohort were plotted: the x-axis represents the predicted probability of developing elevated SUA levels, and the y-axis represents the actual probability of developing elevated SUA levels. The diagonal dashed line represents a perfect prediction by an ideal model, and the solid line represents the performance of our model. The closer the solid line is to the diagonal dashed line, the more accurate the model's predictions are.

Application of the Model for Elevated SUA

The above model was simplified into the nomogram shown in Figure 5, and points for the risk category of the outcome can be obtained by calibration with a point caliper and then combined to obtain a total score that can determine the probability of the outcome events. A higher total score indicates a greater risk of elevated SUA levels. For example, if a man aged 75 years has a history of hypertension, diabetes, kidney stones and mild fatty liver; his baseline SUA level, baseline eGFR, and urine pH are 400 μmol/L, 80 mL/min/1.73 m^2 and 7, respectively; and his BMI is 24 kg/m^2, his HDL concentration is 1.6 mmol/L, and he has proteinuria, then the corresponding score will be approximately 33, 14, 22, 4, 20,

Table 2 Sensitivity, Specificity, Cut-off Value and AUC of the Models in Different Populations

	Development Cohort			Validation Cohort		
	Total Population	Male	Female	Total Population	Male	Female
Cut-off value	−2.38	−1.99	−3.28	−1.42	−1.27	−1.80
Sensitivity	0.79	0.67	0.79	0.80	0.69	0.89
Specificity	0.78	0.84	0.77	0.68	0.73	0.68
AUC	0.82	0.80	0.82	0.76	0.77	0.80

Abbreviation: AUC, area under the curve.

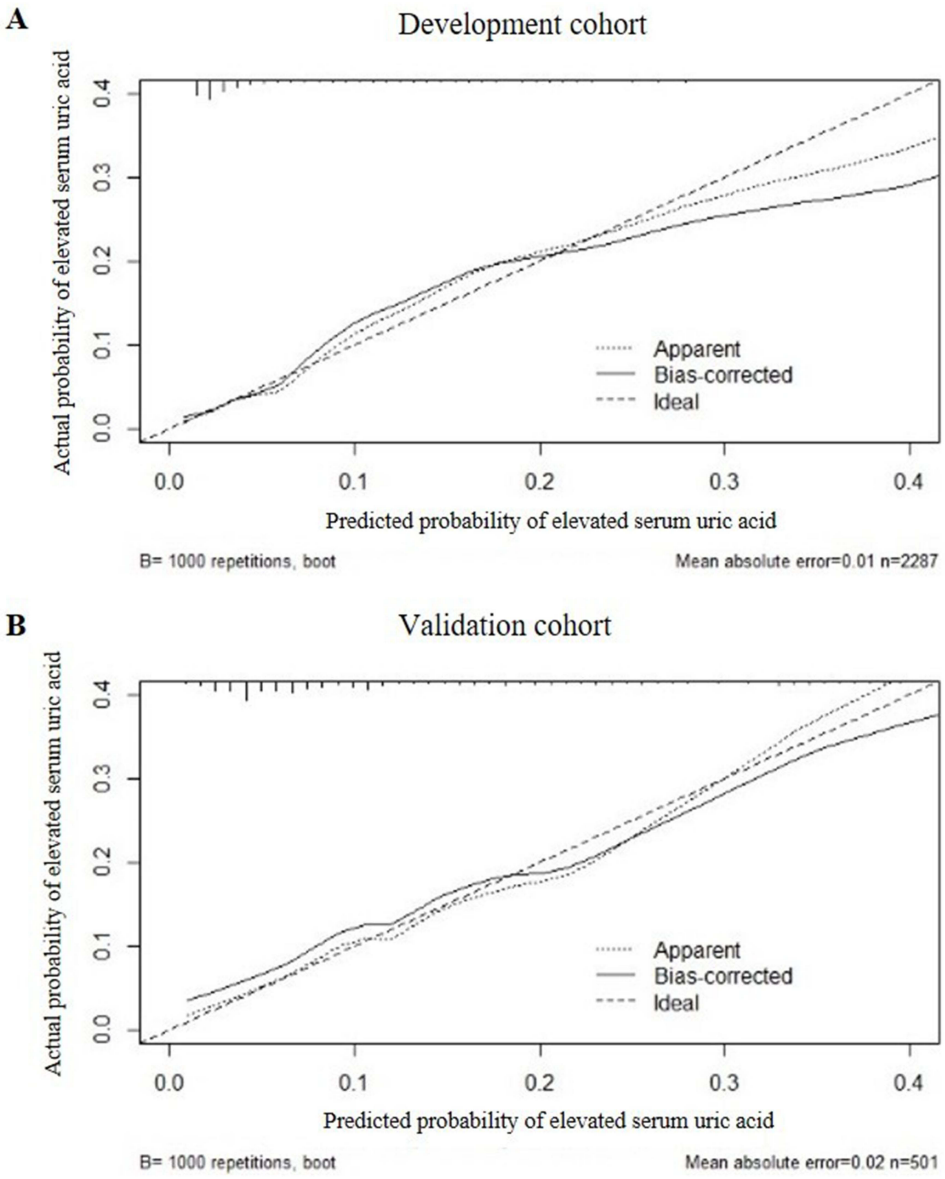

Figure 4 (**A**) Calibration plot for predicting the probability of elevated serum uric acid levels in the development cohort. (**B**) Calibration plot for predicting the probability of elevated serum uric acid levels in the validation cohort.

2, 14, 2, 98, 14, 49, and 10, respectively, according to the order of the indicators on the nomogram. The total score is approximately 282, indicating an estimated probability of elevated SUA next year of 70% for this patient (Figure 5).

Discussion

In this study, we identified independent risk factors for elevated SUA in older adults, and the LR-based risk prediction model developed on this basis showed good discrimination in both the developmental cohort and the external validation cohort. These findings can help clinicians accurately assess the predictive value of relevant risk factors and take appropriate measures to reduce the incidence of HUA in the elderly population.

Prediction models for HUA have been developed for different cohorts, including individuals with type 2 diabetes,[29] diabetic kidney disease,[30] membranous nephropathy,[31] and IgA nephropathy.[32] In a previous study, Lee et al[33] developed a model to predict the potential risk of developing HUA using sex, BMI, and the PPARγ gene. The final model had a sensitivity of 69.3% and a specificity of 83.7%. Although its sensitivity was better than that of the other two models in our study, considering its cost and other factors, it is difficult to apply in the population. Recently, Zeng et al[20] developed

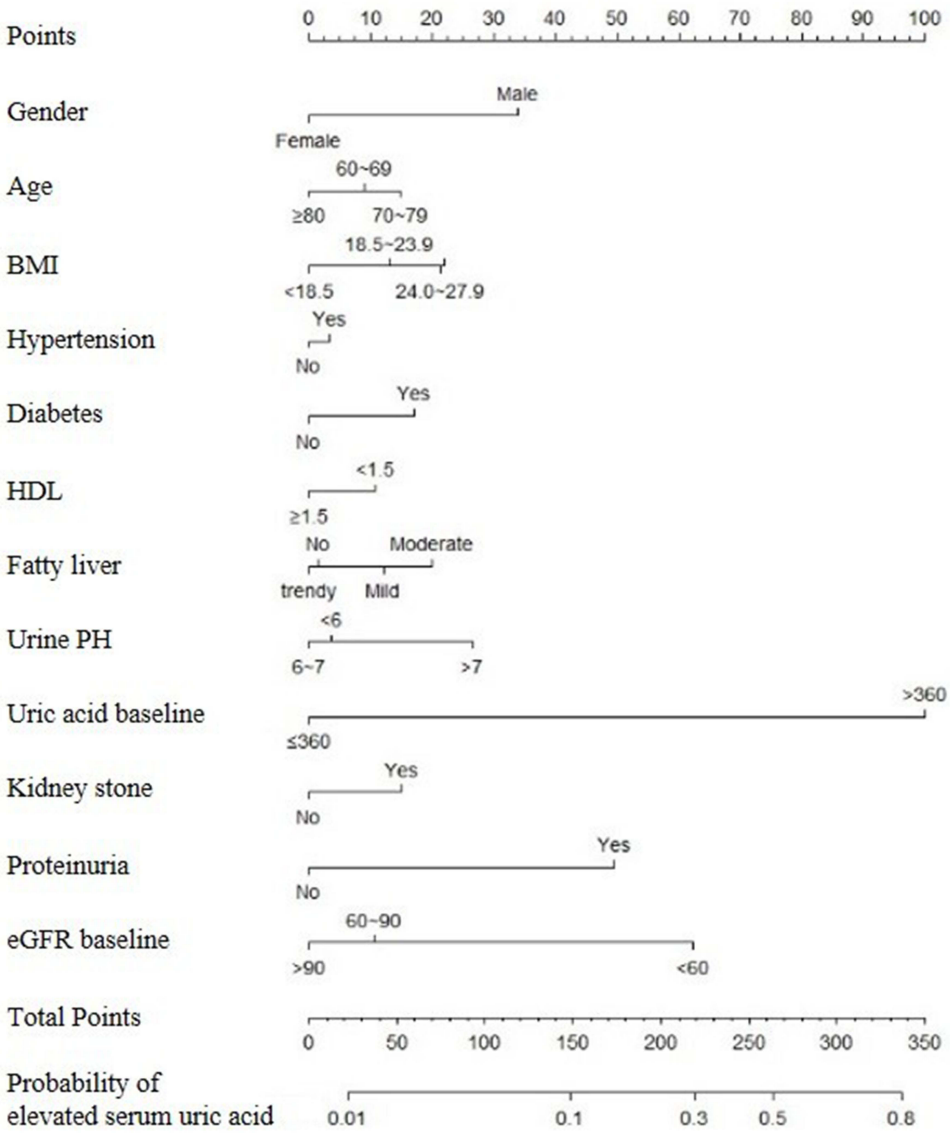

Figure 5 Nomogram for predicting the probability of elevated serum uric acid levels. The presence or absence of each clinical characteristic indicates a certain number of points. The number of points for each clinical characteristic is shown in the top row. The presence of clinical characteristics is associated with several points generated with the nomogram. The points for each characteristic are summed to generate a total-point score. The total points correspond to the probability of elevated serum uric acid levels.

a Fahrenheit index prediction model based on dietary information on vegetable, meat, and egg intake from 1488 residents and obtained a neural network model with an AUC of 0.827, a sensitivity of 75%, and a specificity of 86%. The AUC and sensitivity of this Fahrenheit model were better than those of the other two models in our study, but the model structure was more complex, needed more statistical background knowledge from the operator, and needed the inclusion of more variables. In another study, a diagnostic model for predicting HUA was established based on gut microbiome alterations in individuals with different SUA levels.[34] The model was not only time-consuming and laborious when applied in the clinic but also prone to recall bias. Several researchers have identified new markers, such as reduced serum interleukin-38 levels, for the clinical diagnosis and risk prediction of HUA;[35] however, these findings need to be further confirmed. Compared with the abovementioned two prediction models, our prediction model has easier access to key information and comparable prediction performance. Compared with that of another prediction model for the development of HUA based on a population of 58,542 northern urban-dwelling Chinese individuals with a C statistic of 0.783 (95% CI, 0.779–0.786) for men and 0.784 (95% CI, 0.778–0.789) for women,[19] the predictive efficacy of our prediction model was greater (C statistic for men =0.801; C statistic for women =0.821).

The nomogram (Figure 5) provides a tool for the visual representation of predictive models. Previous studies have shown that the nomogram model outperforms other machine learning models (artificial neural networks and classification tree models) in terms of accuracy and clinical utility.[36,37] The establishment of visual predictive models may help physicians identify those at high risk of developing HUA in the elderly population at an early stage to develop earlier and more effective intervention strategies for high-risk patients, such as UA-lowering treatment, lifestyle modification, and increased frequency of follow-up, thereby reducing the occurrence of gout and other complications. For low-risk patients, unnecessary drug therapy can be reduced to avoid drug-related adverse effects. However, patients' clinical information and laboratory test results are often incomplete or of low quality, which may affect the accuracy of the column chart. Even if the chart can accurately predict the risk of developing HUA, the willingness of patients to comply with the doctor's advice, lifestyle changes, and regular follow-up is still a major challenge in clinical management.

Our study revealed that the risk of elevated SUA was 1.90 times greater in men than in women (95% CI, 1.28–2.85), which is consistent with the findings of a previous meta-analysis.[14] Similarly, in a general population cohort study from the Beijing–Tianjin–Hebei (BTH) region in China, after adjusting for the effect of regional factors, the prevalence of HUA was greater in men (18.94%) than in women (16.90%) in the 60–80 years age range.[38] However, another retrospective analysis of 1052 diabetic patients aged >70 years from Shanghai revealed that the overall prevalence of HUA was 21.10%, and the prevalence of HUA in women (24.91%) was greater than that in men (16.53%). These findings suggest that lower estrogen (E) levels in women are among the factors contributing to the greater prevalence of HUA in women than in men.[39] Studies have shown that the prevalence of HUA in women increases with age, changing dramatically from the age of 50 and peaking at age 70.[14] Elevated SUA was found to be associated with both natural and surgical menopause.[40,41] The dramatic decrease in vitamin E after menopause was accompanied by an increase in UA, suggesting a potential protective effect of vitamin E against HUA. The administration of conjugated equine oestrogen combined with medroxyprogesterone actuate therapies were associated with significantly decreased UA levels in postmenopausal women.[42] Analysis of kidney samples from ovariectomized mice subjected to vitamin E replacement revealed that E inhibited the expression of UA transporter proteins such as UA transporter 1 (URAT1), glucose transporter 9 (GLUT9), and ATP-binding cassette subfamily G member 2 (ABCG2), leading to decreased UA excretion.[43] In addition, a healthy lifestyle reduces the risk of developing HUA by 41%, whereas men who consume a high-calorie, high-purine diet and excessive alcohol are more likely to develop HUA.[44]

Notably, studies have shown that the associations between HUA status and the risk of developing cardiovascular disease or metabolic diseases are stronger in women.[45–47] A cohort study from Taiwan revealed that in women, but not in men (P=0.93), SUA levels were significantly associated with the insulin resistance index after controlling for age, BMI and GFR (gamma=0.117, P=0.012).[45] This finding suggested that clinicians should not ignore the risk of abnormally high SUA levels in women just because male sex is a risk factor for abnormally high SUA levels.

In the present study, the risk of developing abnormal SUA levels was 2.56 times greater in participants with proteinuria than in those without proteinuria (95% CI: 1.44 to 4.43). This phenomenon has not been reported in previous studies. The mechanism may be associated with an increased likelihood of proteinuria in people presenting with metabolic syndrome,[39,48] whereas the presence of abnormally high SUA levels is closely associated with the risk of developing metabolic syndrome. In addition, the presence of proteinuria suggested that there may be some structural and functional damage to the kidney, which may influence renal UA excretion, but this still needs to be explored in further relevant studies.

Our study suggested that a decreased eGFR is a risk factor for abnormally high UA levels, which is consistent with the findings of previous studies.[49,50] A study from the United States showed that the ORs for the development of gout and HUA were 5.9 (95% CI: 2.2 to 15.7) and 9.58 (95% CI: 4.3 to 22.0), respectively, among those with severe renal impairment compared with those with no renal impairment;[49] moreover, the relationship between renal impairment and the prevalence of HUA and gout was nonlinear, but the trend increased with increasing severity of renal function decline.[50] The underlying cause of this finding may be the development of HUA in CKD stages G3-5 as UA clearance decreases.[51] Other reasons for this could include the increased use of certain medications by elderly individuals with CKD, including diuretics, aspirin, and immunosuppressants, which can impair the renal clearance of UA.[52]

In our study, diabetes was an additional risk factor for women. In contrast to previous findings, a study from Chengdu, China, which included 1035 older adults aged 80 to 100 years, revealed that HUA status was not associated with the risk

of developing hyperglycemia.[53] Another study from Tianjin, China, revealed that diabetes did not increase the risk of developing HUA, and there was even a negative correlation in the diabetes group among male participants (OR=0.811, *P*=0.002).[18] This finding corroborates the findings of previous studies in which diabetic patients with glycosuria had a zero prevalence of HUA and excreted more UA than did patients without glycosuria.[54] Chino et al also reported that SGLT2 inhibitor-induced glycosuria in the proximal tubule may inhibit UA reabsorption.[54] Glycosuria induced by elevated blood glucose levels in diabetic patients may lead to competitive inhibition of UA reabsorption. However, the relationship between DM and SUA remains controversial. Some studies have reported that SUA can cause pancreatic β-cell dysfunction, making HUA an independent risk factor for type 2 DM.[55,56] Notably, previous studies have generally used different diagnostic criteria for HUA, such as SUA >420 μmol/L in men and >360 μmol/L in women.[57] In addition, our study revealed sex differences in the ability of diabetes mellitus to predict HUA, and whether there is an interaction effect between DM status and hormone levels remains to be further explored.

The strengths of this cohort study include the use of a risk prediction model in a unique geriatric cohort and external validation, which showed good performance. In addition, the predictors in our model are easily available anthropometric and blood biochemical biomarkers, which are more accurate than questionnaire variables for avoiding memory bias.

The limitations of our study should be mentioned. First, the participants in our study were all urban-dwelling elderly individuals; therefore, our prediction model may not be applicable to other populations. Therefore, a larger range of external validation of the risk prediction model is needed. Second, our results are based on one-time measurements, which may not accurately reflect the status of participants and may overestimate the prevalence of HUA. Finally, we did not incorporate additional older-adult HUA predictors, such as dietary habits,[58] smoking status,[59] sedentary behavior, or physical activity,[60] into the model. Owing to these limitations, in the present study, we may not have covered all risk factors, and we failed to explore factors in rural areas in China; however, as HUA is more commonly detected in clinical practices in urban cities, data on the living habits and SUA levels of rural-dwelling patients are not always available. Therefore, our nomogram may be more applicable in real-world clinical practice.

Conclusion

In this study, we identified the risk factors for abnormally elevated SUA levels in elderly individuals via simple physical examination indicators and established a corresponding prediction model. This model may help clinicians identify high-risk groups in time for early intervention and provide some assistance in the prevention and control of chronic diseases associated with elevated SUA levels.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

All the authors declare that there are no conflicts of interest.

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