Central precocious puberty risk prediction model for Chinese children: a cross-sectional study

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Abstract

Objective The aim of this study was to explore the risk factors of central precocious puberty (CPP) in children, furthermore, develop and evaluate the risk prediction model in CPP children.

Methods A cross-sectional study based on the electronic medical record system was conducted in the Children Health Care Center in a tertiary A-level hospital in China. A total of 187 children agreed to participate the study from August 2020 to July 2021. Children were split into the central precocious puberty group (n=52) and non-precocious puberty group (n=135), the collected variables associated with CPP (P<0.05) in univariate analyses were introduced in logistic regression analysis to construct the risk prediction model. Then a nomogram was built to visualize the model, and the receiver operating characteristic (ROC) curve was used to predictive the effect of the model.

Results The risk factors of CPP children in the risk prediction model were bodyweight (*OR*=2.383), entertainment time for electronic devices (*OR*=0.042), sweet tooth (*OR*=12.400), fried food lover (*OR*=8.696), and intake of carbonated soft drinks (*OR*=15.816). The area under the ROC curve (AUC) was 0.874 (95% CI: 0.817-0.931), the sensitivity was 0.852, the specificity was 0.769, the Youden index was 0.621, and the optimum critical value was 0.960.

Conclusions The nomogram risk prediction model can effectively predict the CPP occurrence in children and provide references for clinical evaluation and early intervention.

Introduction

According to the data released by the China Association of Health Promotion and Education in 2018, there are about 530,000 children with precocious puberty (PP). A survey in South Korea showed that the incidence of PP among girls under the age of nine rose from 89.4/100,000 in 2008 to 415.3/100,000 in 2014[1]. Central Precocious puberty (CPP), the main type of precocious puberty (PP), is a pediatric endocrine disease. The main mechanism of this disease is that the hypothalamus increases the secretion of gonadotropin-releasing hormone (GnRH) in advance, then activates the function of hypothalamic-pituitary-gonadal (HPG) axis, causing the development of secondary sexual characteristics before the age of 9 years in boys and 8 years in girls, or the onset of menstruation before 10 years[2]. Notably, the prevalence of CPP is a serious health issue in children worldwide[3], predicting which children will develop these phenotypes carries substantial social value.

CPP not only affects the physical and mental health of children but also brings various social problems. Children with CPP are usually at school age, a crucial period for their growth and cognitive development. The early appearance of secondary sexual characteristics and menstruation causes a lot of inconvenience to the child's life, leading to psychological and behavioral problems, such as low self-esteem, social withdrawal, and violation of discipline[4]. In addition, the family is the main caregiver and supporter, parents of CPP children are worried about the adverse effects of hormone disorders on

children's future life and endure the psychological burden[5]. Furthermore, the gold standard for CPP diagnosis is GnRH stimulation test, a time- and money-consuming test, and long-term treatment and nursing are more difficult for ordinary families to afford, which will damage the harmonious family relationship. Therefore, establishing a simple early risk prediction model for CPP children is paramount in family-centered pediatric nursing care, tailoring treatment to surveil and intervene will optimize outcomes for children with CPP.

Risk prediction models have been used in other diseases and provide a convenient way to identify high-risk individuals. However, there are few related studies in China, and the risk prediction model of CPP has not been reported. The purpose of this study was to establish a CPP nomogram risk prediction model for prevention and early intervention and to provide a convenient assessment tool for clinicians and parents.

Materials And Methods

Study population

187 children were selected from the electronic medical record system who came to the Children Health Care Center in a tertiary A-level hospital, Hunan, China, from August 2020 to July 2021. According to clinical diagnosis, they were divided into the CPP group (n=52) and the non-precocious group (n=135). Inclusion criteria: children aged from 4 to 9 years old and parents signed informed consent. Exclusion criteria: congenital hypothyroidism, congenital adrenal hyperplasia, gonadal tumor, other organic basic diseases, and unable to cooperate with the investigation. This study has been approved by the Ethics Committee of Hunan Normal University, and informed consent was obtained from all subjects and their legal guardians.

Patient and public involvement

Patients and the public were not directly involved in the design, recruitment, or evaluation of this study. Results from the paper will be disseminated to the public through online article format.

CPP diagnostic standard

Reference to the *Guidelines for diagnosis and treatment of central (true) precocious puberty*[6], the specific diagnostic criteria are as follows: (1) secondary sexual characteristics appear before 8 years old in girls and 9 years old in boys; (2) serum gonadotropin and sex hormone reached adolescent level; (3) gonadal enlargement (B-ultrasound: multiple follicles with diameter>4 mm, ovarian volume>1 ml in girls; testicular volume≥4 ml in boys); (4) bone age exceeds chronological age at least 1 year. All children were evaluated by three physicians according to the guidelines and uniform criteria to ensure the accuracy and consistency of diagnosis.

Data collection

Before collecting the data, all researchers were trained centrally and uniformly, then explained the research purpose to the subjects' parents. The general information questionnaire included the child's basic demographic data, such as age, gender, residence, living and eating habits, parents' occupation, and so on. The investigators distributed and collected the questionnaires on-site, and checked them item by item. In addition, the growth and development parameters, including height, bodyweight, body mass index, bone age, gonadotropin, and sex hormone were achieved from the hospital's electronic medical record system.

Statistical analysis

The enumeration data were presented as numbers (percentage), the measurement data were presented as mean ± standard deviation (SD), and compared between two groups using $\chi 2$ test and *t*-test, respectively. Variables with *P* values less than 0.05 in the univariate analysis entered the multivariable logistic regression model. Then, the logistic regression equation was used to evaluate the association between potential predictors and CPP and construct a risk prediction model. In the nomogram risk score system, the risk for CPP was demonstrated by total points which were calculated according to the logistic regression model, the area under ROC curve (AUC) was used to evaluate the predictive efficiency of the model, the performance was assessed by calibration. IBM SPSS 22.0 (IBM Corp; Armonk, NY) and R software version 3.6.3 (Vienna, Austria) were used for all statistical calculations and modeling.

Results

Univariate analysis of CPP in children

The univariate analysis results show that the difference of some parameters was statistically significant ($P<0.05$) between the CPP group and non-precocious group. These indicators included bone age, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol, mother's occupation, father's occupation, only child, left-behind children, family history of CPP, entertainment time for electronic devices, sweet tooth, fried food lover, intake of carbonated soft drinks, and time for outdoor exercise every day. A detailed description was shown in Table 1.

Table 1 Comparison of risk factors related to CPP in children [`c±s or n(%)]

Variable	Central precocious puberty group (*n*=52)	Non-precocious group (*n*=135)	t/c^2	*P*-value
Age (year)	7.60±1.18	7.64±1.24	-0.204	0.838
Height (cm)	132.77±10.28	127.86±13.10	2.429	0.016
Bodyweight (kg)	34.38±5.65	25.16±2.68	11.296	0.001
BMI (kg/m^2)	15.76±0.92	15.72±1.01	0.251	0.802
Bone age (year)	8.37±1.52	7.64±1.24	3.365	0.001
LH (IU/L)	5.28±2.00	1.08±0.63	14.844	0.001
FSH (IU/L)	16.87±2.57	2.47±2.03	36.282	0.001
Testosterone (ng/dL)	1.34±0.97	2.69±0.75	-10.089	0.001
Estradiol (pmol/L)	35.23±10.18	17.24±5.50	12.085	0.001
Gender (%)				
Male	3 (5.77)	7 (5.19)	0.025	0.001
Female	49(94.23)	128(94.81)		
Career of mother (%)				0.874
Self-employed household	15(28.85)	6 (4.44)	33.584	
Public institution worker	22(42.31)	108(80.00)		
Other	15(28.84)	21 (15.56)		
Career of father (%)				0.001
Self-employed household	32(61.54)	19 (14.08)	69.491	
Public institution worker	11(21.15)	114(84.44)		
Other	9 (17.31)	2 (1.48)		
Residence (%)				0.001
Country	22(42.31)	65 (48.15)	0.515	
City	30(57.69)	70 (51.85)		
Only child (%)				
No	19(36.54)	80 (59.26)	7.779	0.473
Yes	33(63.46)	55 (40.74)		
Left-behind children (%)				

No	27（51.92）	98 （72.59）	7.237	0.005
Yes	25（48.08）	37 （27.41）		
Family history of CPP (%)				
No	48（92.31）	133（98.52）	4.663	0.007
Yes	4 （ 7.69 ）	2 （ 1.48 ）		
Using adult skincare products (%)				
No	50（96.15）	134（99.26）	2.293	0.031
Yes	2 （ 3.85 ）	1 （ 0.74 ）		
Watching love cartoon (%)				
No	40（76.92）	109（80.74）	0.338	0.188
Yes	12（23.08）	26 （19.26）		
Time for electronic devices (%)				
≤7 h/w	35（67.31）	46 （34.07）	16.887	0.561
＞7 h/w	17（32.69）	89 （65.93）		
Sleep duration (%)				
≤9 h/d	9 （17.31）	14 （10.37）	1.675	＜ 0.001
＞9 h/d	43（82.69）	121（89.63）		
Outdoor exercise duration (%)				
≤2 h/d	30（57.69）	48 （35.56）	7.566	0.196
＞2 h/d	22（42.31）	87 （64.44）		
Sweet tooth (%)				
No	12（19.23）	106（78.52）	49.559	0.006
Yes	40（80.77）	29 （21.48）		
High-protein foods lover (%)				
No	11（21.15）	32 （23.70）	0.138	＜ 0.001
Yes	41（78.85）	103（76.30）		
Fried foods lover (%)				
No	22（42.31）	105（77.78）	21.674	0.710
Yes	30（57.69）	30 （22.22）		

Carbonated beverage intake (%)	21（40.38）	108（80.00）	25.169	
≤500 ml/w	31（59.62）	27 （20.00）		0.001
（500 ml/w	5 （ 9.62 ）	28 （20.74）	3.197	
Milk intake (%)	47（90.38）	107（79.26）		
≤2 000 ml/w				0.001
（2 000 ml/w				
				0.074

BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone.

Predictors of CPP children

12 variables (*P*（0.05) in univariate analysis were introduced in logistic regression. The independent variables were assigned as follows: parents' occupation: 1=Self-employed household, 2=Public institution worker, 3=Other; only child, left-behind children, family history of CPP, sweet tooth, and fried food lover: 1=No, 2=Yes; time for electronic devices: 1=≤7 h/w, 2=（7 h/w; outdoor exercise duration: 1=≤2 h/d, 2=（2 h/d; and carbonated soft drinks intake: 1=≤500 ml/w, 2=（500 ml/w, height and bodyweight were entered by original values. The results showed that intake of carbonated soft drinks was the strongest predictor of CPP (*OR*=15.816, 95% CI: 0.817-0.931); bodyweight, entertainment time for electronic devices, preference for sweets and fried food were the risk factors for CPP in children (*P*（0.05). Detailed data was displayed in Table 2.

Table 2 Predictors of CPP children in logistic regression analysis（*n*=187）

variable	*β*	*SE*	*Wald* c^2	*P-value*	*OR*	95% *CI*
Constant	-4.861	1.435	8.508	0.004	-	-
Bodyweight	0.868	0.304	8.170	0.004	2.383	1.314-0.321
Fried food lover	3.165	1.176	7.245	0.007	0.042	0.004-0.423
Sweet tooth	4.820	1.925	6.270	0.012	12.400	2.850-33.961
Time for electronic devices	2.163	1.076	4.042	0.044	8.696	1.056-17.636
Carbonated beverage intake	2.761	1.337	4.267	0.039	15.816	1.152-21.716

95% CI: 95% confidence interval, OR: odds ratio; SE: standard error.

Build a risk prediction model and analyze the prediction effect

According to the prediction model formula[7], the risk prediction model of CPP in children was *P*=1/{1+exp[-(0.868×bodyweight + 3.165×time for electronic devices + 4.820×sweet tooth + 2.163×fried food lover + 2.761×carbonated soft drinks intake)]}, and build a nomogram (Fig.1A). Calibration curve almost coincided with the ideal curve (Fig.1B). the AUC was 0.874 (95% CI: 0.817-0.931), the sensitivity was 0.852, the specificity was 0.769, the maximum value of Yoden index is 0.621, and the best critical value is 0.960 (Fig.1C).

Discussion

Premature puberty (PP) in children is divided into central precocious puberty (CPP) and peripheral precocious puberty (PPP) according to whether HPGA is initiated early. The clinical characteristics of CPP are that growth and development mismatch with age, bone age exceed chronological age, and the levels of sex hormones are abnormal[8]. In this study, 187 children were tested for age, height, bodyweight, BMI, bone age, and sex hormone levels, the results showed that height, bodyweight, bone age, LH, FSH, and estradiol were higher in 52 children with CPP than those in non-precocious puberty children. These clinical manifestations were consistent with the diagnostic criteria of CPP in children.

In our research, overweight was an independent risk factor for CPP in children (*OR*=2.383), the same result was found in the previous study[9]. It may be that energy balance and HPGA modulate some common neuroendocrine regulatory factors, such as leptin, adrenaline, neuropeptide[10]. In terms of the global, the incidence of overweight and obesity in children is increasing year by year, the age of puberty is earlier and the duration is getting shorter and shorter. Early and reasonable weight control not only improves children's physical and mental health but also cultivates good social relationships. Parents should pay more attention to their children's weight changes, actively improve living habits and eating habits, make detailed and personalized dietary and exercise plans. It is necessary to ensure that children receive essential nutrients but avoid obesity, parents realize the importance of physical examination in children's growth and development.

In addition, the results in our study showed that the risk of CPP in children who used electronic products for a long time (≥7 h/w) was 1.13 times higher than that of short-term users. Long-term use of electronic equipment was a risk factor of CPP in children (*OR*=0.042). It was demonstrated that the light from electronic products such as TV, computer, mobile phone, phone watch can significantly reduce the levels of melatonin, weaken the inhibition on gonads, so as to induce the occurrence of CPP[11]. Therefore, for parents, overusing electronic products instead of themselves to accompany children may not be the best choice. They should make scientific guidance and appropriate intervention in children's use of electronic products, encourage and support children to participate in various outdoor activities, and cultivate their self-control and self-management ability.

The occurrence of CPP in children was closely related to whether they like sweets (*OR*=12.400) or fried food (*OR*=8.696), which is similar to the results of Yu *et al*[12]. Sweets and fried foods often contain some additives such as thickeners, emulsifiers, baking powder, puffing agents, which have low nutrition but high energy. Bingeing is prone to induce obesity, unbalanced diet and severe food preference. It not only affects digestion and absorption, triggering diabetes, cardiovascular disease, cancer, but also produces the early appearance of secondary sex characteristics. Hence, parents should reasonably control the children's diet, try not to eat high salt, animal fat, red meat, sugar-sweetened drinks, low fiber vegetables; conversely, exercise, low-calorie diet, vegetables, fruit, legume, and fish are conducive to maintain the balance between hygiene and nutrition, and provide the necessary dietary nutrition for children's growth and development. Besides, according to the nomogram, another diet-related risk factor was the intake of carbonated soft beverages (≥500 ml/w, *OR*=15.816). Carbonated soft beverages are mainly composed of additives and preservatives, such as artificial colors, methylparaben, propylparaben, and sugar. When these endocrine disruptions accumulate in the body to a certain extent, they will produce estrogen-like activity, resulting in the advancement of normal menstrual cycle[13]. Furthermore, a large amount of carbonated soft drinks not only increase the risk of dental caries and gastrointestinal damage, but also affect the absorption of vitamins, minerals, and other nutrients, which has become one of the most important factors in hindering the growth and development of children. Therefore, it is necessary for parents to guide children to drink enough water and milk instead of milk beverages.

The calibration curve showed good consistency in the risk prediction model. We used AUC to quantify the model predictive performance. AUC≥0.9 indicates high accuracy; 0.7-0.9, medium accuracy; 0.5-0.7, low accuracy[14]. In our study, AUC of the risk prediction model was 0.874, the sensitivity was 0.852, and the specificity was 0.769, which indicated that this model could be used to predict and identify CPP in children. Parents and caregivers can systematically assess children's development, living and eating habits based on our risk prediction model, and then formulate a prospective health guidance program, and implement targeted early interventions measures for children.

Conclusion

This study found that long-term (≥7 h/w) use of electronic devices, sweet tooth, fried food lover, and large intake (≥500 ml/w) of carbonated soft drinks were risk factors for central precocious puberty in children. The risk prediction model constructed in this study showed perfect predictive efficacy and could be applied in the physical examination of children, providing references for clinical evaluation and early intervention, and suppling convenient for parents and clinicians to carry out scientific prevention and control measures. Validations in other settings are needed before the adoption in clinical practice.

Abbreviations

BMI: Body mass index; PP: precocious puberty, CPP: Central precocious puberty; ROC: receiver operating characteristic; HPGA: Hypothalamic-pituitary-gonadal axis; PPP: Peripheral precocious puberty; LH:

Luteinizing hormone; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; CI: Confidence interval.

Declarations

Author contributions

Ying Wu and Jing Wen contributed to the concept and design of the study. JiaYang Yuan, Wenzhuo Huang and Lijuan Liu took responsibility for the data collection. Li Cong and Ying Wu performed the statistical analysis and wrote the manuscript. All authors made substantial contributions to data acquisition, results interpretation, and critical revisions to the manuscript for important intellectual content.

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Availability of Data and Materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

All experimental protocols in this study were approved by the Ethics Committee of Hunan Normal University (approval No. 2019172), and all methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects and their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

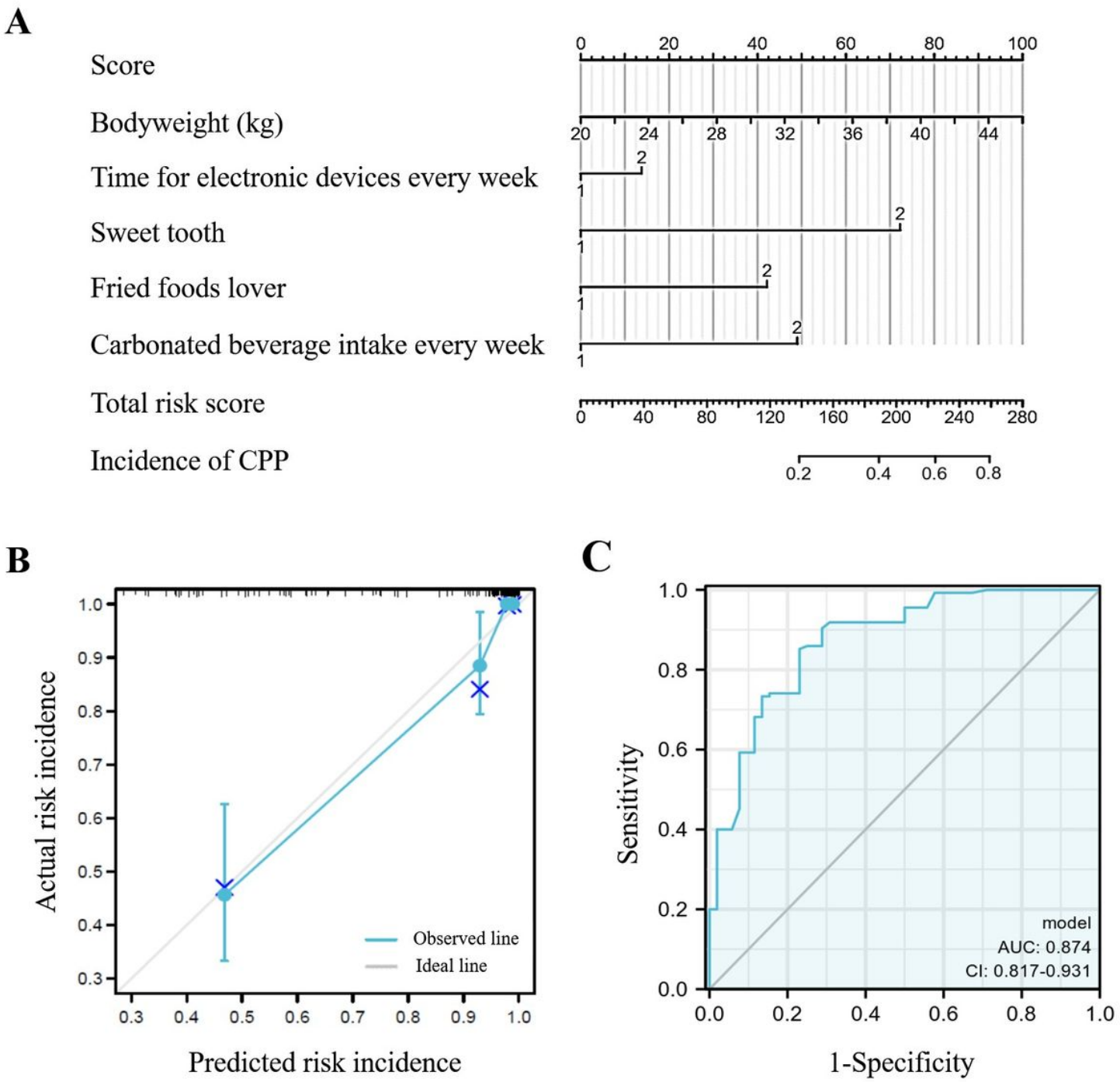

Figure 1

Visualization and effect verification of the CPP risk prediction model in Chinese children. A: Nomogram of the risk prediction model. A total score was calculated by adding each single score and, by projecting the total score to the bottom scale, the incidence of CPP was predicted. **B:** Calibration plot of the nomogram. X-axis was nomogram predicted probability, and Y-axis was observed, the curve was close to the diagonal and almost coincided with the ideal line. **C:** ROC curve of the risk prediction model. The area under the ROC curve was 0.874 (95% CI: 0.817-0.931), the model showed higher accuracy in the risk prediction.

Supplementary Files

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- SupplementaryMaterialData.xlsx