Multivariate predictive model of the therapeutic effects of metoprolol in paediatric vasovagal syncope: a multi-centre study

Yaxi Cui,[a,e] Jing Zhang,[b,e] Yuwen Wang,[c,e] Ying Liao,[a,e] Keyu Liu,[a] Wenrui Xu,[a] Shu Wu,[a] Chufan Sun,[a] Chunyu Zhang,[a] Qingyou Zhang,[a] Ping Liu,[a] Yuli Wang,[a] Yanjun Deng,[b] Chen Shen,[b] Yao Lin,[b] Hong Cai,[c] Juan Zhang,[c] Runmei Zou,[c] Ping Liu,[c] Shuo Wang,[c] Hongfang Jin,[a,*] Lin Shi,[b,***] Cheng Wang,[c,**] and Junbao Du[a,d,****]

[a]Department of Pediatrics, Peking University First Hospital, Beijing, 100034, China
[b]Department of Pediatric Cardiology, Children's Hospital, Capital Institute of Pediatrics, Beijing, 100020, China
[c]Department of Pediatric Cardiovasology, Children's Medical Center, The Second Xiangya Hospital, Central South University, Changsha, Hunan, 410011, China
[d]State Key Laboratory of Vascular Homeostasis and Remodeling, Peking University, Beijing, 100191, China

eBioMedicine
2025;113: 105595
Published Online xxx
https://doi.org/10.1016/j.ebiom.2025.105595

Summary

Background Metoprolol therapy for paediatric vasovagal syncope (VVS) has yielded inconsistent results, necessitating predictive markers. We aimed to develop and validate models to identify paediatric VVS patients likely to benefit from metoprolol.

Methods 478 metoprolol-treated paediatric patients with VVS were enrolled from three syncope units and divided into retrospective training (March 2017–March 2023, n = 323) and prospective validation cohorts (April 2023–March 2024, n = 155). Fourteen patients (2.9%) were excluded for lacking follow-up data. Patients were classified as responders or non-responders based on symptom improvement after 1–3 months of metoprolol therapy. Univariate analysis and logistic regression were used to select the candidate predictors. A nomogram and a scoring model were established to predict treatment efficacy. The model values were analysed using a receiver operating characteristic (ROC) curve. Consistency was evaluated using the Hosmer–Lemeshow (H-L) test, calibration curve, and concordance index (C-index). The clinical utility of model was assessed through the decision curve analysis (DCA). Internal validation was performed using the bootstrap approach. The predictive model derived from the training cohort was validated in the validation cohort to assess its accuracy and feasibility.

Findings Increased heart rate during positive response in head-up tilt test (ΔHR), corrected QT interval dispersion (QTcd), and standard deviation of all normal-to-normal intervals (SDNN) were selected as independent predictors to develop a predictive model. A nomogram model was built (AUC: 0.900, 95% CI: 0.867–0.932); the H-L test and calibration curves showed a strong alignment between predicted and actual results. The scoring model was established in the training cohort (AUC: 0.941, 95% CI: 0.897–0.985), yielding a sensitivity of 82.8% and a specificity of 96.5%, with a cut-off value of 2.5 points. In the external validation cohort, the scoring model achieved a sensitivity, specificity, and accuracy of 93.6%, 80.9%, and 87.7%, respectively.

Interpretation The nomogram and scoring model were constructed to predict the efficacy of metoprolol for children with VVS, which will greatly assist paediatricians in the individual management of VVS in children and adolescents.

Funding This research was funded by National High-Level Hospital Clinical Research Funding (Clinical Research Project of Peking University First Hospital, grant number 2022CR59).

*Corresponding author.
**Corresponding author.
***Corresponding author.
****Corresponding author. Department of Pediatrics, Peking University First Hospital, Beijing, 100034, China.
E-mail addresses: jinhongfang51@126.com (H. Jin), wangcheng2nd@csu.edu.cn (C. Wang), shilin9789@126.com (L. Shi), junbaodu1@126.com (J. Du).
[e]They contributed to the manuscript equally.

Keywords: Children; Multi-centre study; Vasovagal syncope; Metoprolol; Effectiveness; Predictive model

Research in context

Evidence before this study

Vasovagal syncope (VVS), which is the predominant reason for syncope among paediatric patients, significantly jeopardises patient safety and well-being because of its unpredictability. In the previous studies, the use of metoprolol for treating paediatric VVS produced inconsistent outcomes, highlighting the necessity to identify predictive markers to personalise treatment approaches.

Added value of this study

We discovered that the combination of an increased heart rate (HR) during positive response in head-up tilt test (HUTT) compared with baseline value (ΔHR), corrected QT interval dispersion (QTcd), and standard deviation of all normal-to-normal intervals (SDNN) can predict the efficacy of metoprolol treatment for VVS in children and adolescents. Furthermore, we developed a nomogram and a scoring model based on these indicators to facilitate clinical application and guide paediatricians in VVS management in children.

Implications of all the available evidence

We developed a nomogram and scoring model with a high predictive accuracy and convenience for clinical use. The predictive models might not only enhance the likelihood of treatment success but also minimize unnecessary medication exposure in children with VVS.

Introduction

In children and adolescents, vasovagal syncope (VVS) is characterised by short-term loss of consciousness caused by an autonomic reflex-mediated response.[1] It is often associated with postural changes, emotional stress, or various triggers, leading to a sudden decrease in blood pressure (BP) and/or heart rate (HR).[2] Symptoms of VVS often occur abruptly, last for a brief period, and is self-limiting.[3] The primary age range for VVS onset in children is 5–18 years, with peak incidence occurring around puberty. Studies have reported that at least 15%–20% of children and adolescents experience at least one episode of syncope.[4] The incidence of symptom recurrence within 5 years ranges from 33% to 51%.[5] Recurrent episodes of VVS can lead to significant quality-of-life impairments in children, including physical injuries from falls and disruptions to daily activities like school attendance. Some studies also indicate that severe VVS can negatively affect cognitive performance and emotional well-being, particularly when syncopal episodes are frequent or traumatic.[6]

In terms of treatment, non-pharmacological treatment remains the cornerstone of managing VVS, with lifestyle modifications such as increased fluid and salt intake, physical counterpressure maneuvers, and orthostatic training playing a pivotal role in preventing syncope episodes.[7] These approaches are considered the first line of defense due to their simplicity and minimal side effects. Pharmacological interventions, on the other hand, are typically reserved for patients with more severe or refractory cases, where non-pharmacological measures alone are insufficient. However, their effectiveness can vary significantly between individuals.[5] Given the inconsistent outcomes with therapies using medicines, further systematic research is required to better understand which patient groups benefit most from specific treatments, and to optimize management strategies in difficult-to-treat cases.

Metoprolol, a β-adrenergic receptor blocker (β-blocker), is an important method in the treatments for pediatric VVS, and it remains a subject of interest due to its theoretical basis in blocking β-adrenergic receptors, which could modulate the cardiovascular responses that trigger syncope.[8] Based on previous studies, the effectiveness of metoprolol in treating paediatric VVS is generally reported to be around 20%–50%,[5] with variations across different trials. The reasons for the inconsistent results could be the complex pathogenesis of VVS and non-selective application of the medication treatment.[9] One limitation of earlier researches lies in the relatively small sample sizes and single-centre designs, which can limit the generalizability of findings. Additionally, previous studies have not fully explored the predictors of treatment success, which might contribute to the variability in outcomes. Therefore, the development of predictive models to identify which patients would most benefit from metoprolol could potentially enhance its therapeutic outcomes.[10]

Our research aimed to address these gaps by conducting a multi-centre trial with a larger sample size and more rigorous methodologies. This study aimed to develop predictive models, using a variety of clinical and physiological markers, to better identify which VVS children were most likely to benefit from metoprolol, and validate their practical value in clinical settings. This study would help to improve the precision and overall effectiveness of metoprolol treatment in pediatric VVS, thus offering more personalized therapeutic strategies.

Methods

Study participants

All the paediatric patients included in this study were initially treated at the hospitals' paediatric outpatient clinic and subsequently admitted to the syncope centers for inpatient evaluation and diagnosis. Our study included 478 paediatric patients diagnosed with VVS who received metoprolol treatment from March 2017 to March 2024 across three paediatric syncope units: Peking University First Hospital, Children's Hospital, Capital Institute of Pediatrics, and the Second Xiangya Hospital of Central South University. The study was clearly divided into two distinct cohorts: a retrospective training cohort, which included 323 patients collected from March 2017 to March 2023, and a prospective external validation cohort, which gathered 155 patients from April 2023 to March 2024. These two cohorts were analysed separately, with the retrospective data used for model development and the prospective data applied for validation purposes.

Five patients (1.5%) from the training cohort were lacked follow-up data and nine (5.8%) from the external validation cohort were lost to follow-up. Among the remaining 464 patients, 318 patients were included in the training cohort and 146 patients were included in the external validation cohort. Based on the reduction in symptoms, all children in the training cohort who received metoprolol treatment were divided into responder (n = 173) and non-responder (n = 145) groups, and the external validation cohort was divided into responder (n = 78) and non-responder (n = 68) groups (Fig. 1).

The inclusion criteria included: (1) hospitalized in one of the three participating centres from March 2017 to March 2023 with a confirmed diagnosis of VVS; (2) aged 5–18 years; (3) underwent the entire standardized evaluation protocol, including medical history taking and physical and neurological examinations; and (4) took metoprolol for 1–3 months.

The exclusion criteria included: (1) patients with unclear diagnosis or any other potential causes of transient loss of consciousness, such as those with diagnosed cardiogenic syncope, metabolic disorders, and neurological or cerebrovascular diseases. (2) patients with confirmed heart diseases, such as structural heart disease and cardiomyopathy; (3) patients with contraindications to metoprolol; and (4) patients treated with other medications for VVS (e.g., midodrine hydrochloride, oral rehydration salts) or undergoing autonomic nerve function training; and (5) patients had previously been prescribed metoprolol or any other β-blockers before entering the study.

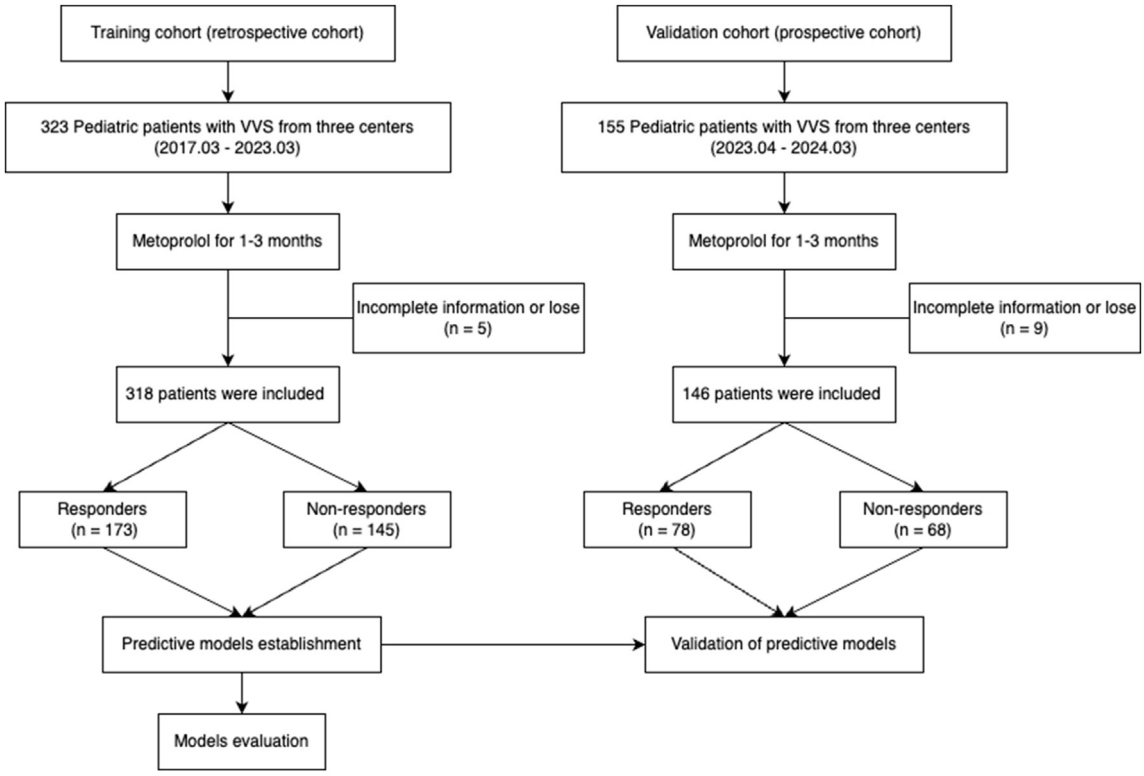

***Fig. 1:* Flowchart of the research.** ROC, receiver operator curve; VVS, vasovagal syncope.

Diagnosis of VVS

VVS was diagnosed based on the following criteria: (1) history of syncope or pre-syncope; (2) possible triggers identified, including prolonged standing, posture changes, sweltering environment, emotional stress, medical interventions, pain, and exposure to stress; (3) a positive reaction during the head-up tilt test (HUTT); and (4) exclusion of any cardiovascular, cerebrovascular, or metabolic diseases.[2,8]

Data collection

We identified potential risk factors indicative of progression to VVS and indicators linked to the therapeutic effect of metoprolol in previous studies.[11–13] These variables were considered potential predictors of metoprolol efficacy. We collected data for an extensive range of variables in patients with VVS, carefully categorised into demographic information (age, sex, height, and weight), clinical history (course of the disease, triggers of syncope, syncopal symptom scores, and pre-syncope symptoms), haemodynamic parameters of HUTT, electrocardiogram (ECG) and 24-h Holter ECG, and echocardiography-related parameters. Personnel across the three centres were uniformly trained to ensure consistency in data measurement standards.

Head-up tilt test

The three centres adopted the same procedure for HUTT, which was conducted with strict adherence to established guidelines and previously published literature.[8] All patients were instructed to empty their bladders after fasting for at least 4 h. The testing environment was maintained in a quiet, warm atmosphere with dim lighting. The study participants lay on a tilt table (Standard SHUT-100A, Jiangsu, China) for at least 10 min and then tilted at a 60° angle. During this period, the operator monitored all vital signs, such as HR, BP, and ECG (Standard SHUT-100A, Jiangsu, China). The equipment for HUTT and continuous monitor used across the three centres was consistent. The duration of the test was contingent on patient responses. A positive reaction prompted immediate termination, whereas in the absence of such a response, the test was extended to a maximum of 45 min. For patients in whom the basic HUTT did not induce syncope or pre-syncope, a subsequent sublingual nitroglycerin HUTT was employed. This procedure entailed an additional 20-min observation following the sublingual administration of nitroglycerin at a dosage of 4–6 μg/kg, with a maximum limit of 300 μg, maintaining the 60° tilt to provoke a response.

The unified criteria for a positive response to VVS during the HUTT included the occurrence of syncopal episodes or pre-syncopal symptoms such as dizziness, headache, sweating, chest tightness, pallor, palpitations, abdominal pain, blurred vision, nausea, and/or vomiting. Additionally, a positive response was indicated by any of the following physiological changes during the HUTT: (1) a drop in systolic blood pressure (SBP) to less than 80 mmHg or diastolic blood pressure (DBP) to less than 50 mmHg, or a decrease in mean blood pressure (MBP) by more than 25%; (2) HR less than 75 bpm for children aged 4–6 years, less than 65 bpm for those aged 6–8-years, and less than 60 bpm for those aged >8 years; and (3) arrhythmias such as sinus arrest, premature junctional contractions, atrioventricular block, and cardiac arrest lasting more than 3 s. These responses were categorised into cardioinhibitory (CI), vasodepressor (VI), and mixed (M) types. VVS-CI was characterized by a notable HR decrease without a significant BP drop, VVS-VI was distinguished by a significant BP decrease without a corresponding decrease in HR, and VVS-M was characterized by decreases in both HR and BP.

Electrocardiogram examination

ECG data were acquired using standard 12-lead ECG machines (GY-5200C, Huanan, China; DMS 300-BTT02, Beijing, China; and FX-7402, Fukuda, Japan) according to a standardised operating procedure. This involved ensuring proper lead labels, stable paper speeds, and clear voltage markers to obtain a reliable baseline. The ECG baseline was required to be stable across 12 leads, with each waveform being distinctly clear and identifiable.[14] The RR interval in sinus rhythm served as the baseline for all measurements. The amplitude of the ECG waveform was recorded starting from the onset of the QRS complex to create a standard reference level.[15] P-wave duration was measured from its onset to its end.[16] The QT interval was measured from the onset of the QRS to the end of the T-wave. If the intersection was unclear, the tangent of the downslope was considered as point of intersection. The primary ECG parameters measured included the maximum and minimum durations of the P wave (Pmax, Pmin) and QT interval (QTmax, QTmin), which are expressed in milliseconds.[17] Corrected P-wave durations (Pcmax and Pcmin) and corrected QT intervals (QTcmax and QTcmin) were obtained by correcting the P-wave and QT interval measurements using the Bazett formula ($Pcmax = Pmax/RR^{1/2}$, $Pcmin = Pmin/RR^{1/2}$, $QTcmax = QTmax/RR^{1/2}$, and $QTcmin = QTmin/RR^{1/2}$). Dispersion indices (Pcd, QTcd) were calculated as the differences between the maximum and minimum readings.[18] Averages were calculated over 3–5 consecutive RR intervals to ensure measurement accuracy and reliability. All electrocardiogram data were measured and calculated by professionals, with an additional person responsible for the verification and correction to ensure the accuracy and stability of the data.

Twenty-four hours Holter monitoring

The analysis of heart rate variability (HRV) was performed by a 3-channel/12-channel Holter under controlled conditions (TLC4000, Qinhuangdao, China;

CT-083S, Hangzhou, China). During the recording period, all participants were hospitalised to minimise external variability and avoid interactions with electronic devices to prevent signal interference. The analysis was strictly limited to normal-to-normal (NN) heartbeats to ensure the accuracy of the interval measurements. The time–domain parameters included the standard deviation of all NN intervals (SDNN), root mean square of successive differences (rMSSD), standard deviation of the average NN interval for all 5-min segments in the entire recording (SDANN), and percentage of successive NN intervals that differed by more than 50 ms (PNN50).[13]

Echocardiography

The primary measurements of interest in echocardiography were the left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS), which served as key indicators of cardiac function and could be influenced by a sympathetic status. LVEF and LVFS were determined by measuring the left ventricle's dimensions at end diastole and end systole using M-mode or 2D echocardiography. To calculate LVEF, it is necessary to measure the volume of blood in the left ventricle at the end of diastole (LVEDV) and the volume of blood remaining in the left ventricle at the end of systole (LVESV). The formula is as follows: LVEF = (LVEDV–LVESV)/LVEDV × 100%. To calculate LVFS, it is necessary to measure the left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD). The formula is as follows: LVFS = (LVEDD–LVESD)/LVEDD × 100%. LVEF and LVFS were expressed as percentages.[11] Experienced cardiologists performed echocardiographic assessments to ensure unbiased results.

Treatment and follow-up

Metoprolol was prescribed solely for the treatment of VVS and not for any other indications or co-morbidities. None of the patients had previously been prescribed metoprolol or any other β-blockers before entering the study. Metoprolol was initiated at a total daily dose of 0.5–1 mg/kg, which is the standard starting range for paediatric patients. The total daily dose was capped at a maximum of either 50 mg per day or 2 mg/kg, whichever was lower. This means that for smaller children, the weight-based dose (2 mg/kg) was the upper limit, while for heavier children, the total dose was limited to 50 mg per day to avoid excessive dosing. The treatment duration ranges from 1 to 3 months, but therapeutic efficacy is assessed specifically at the 3-month mark, ensuring a consistent evaluation period.[8] Follow-up symptoms were documented by professional doctors either in a paediatric cardiology clinic or via telephone. A symptom scoring (SS) system was employed to quantify the frequency of syncopal and/or pre-syncopal episodes both before and at the follow-up endpoint, structured as follows[19]: a score of 0 for the absence of syncopal events, 1 for monthly occurrences, 2 for 2–4 episodes per month, 3 for 2–7 episodes per week, and 4 for daily episodes or more. Patients were classified as responders if they exhibit a reduction of at least one point according to the scoring system employed in the study.

Establishment and evaluation of the nomogram model

A binary logistic regression model was used to distil the variables and develop a nomogram to predict the effect of metoprolol in paediatric VVS. A nomogram is a graphical tool that represents complex mathematical relationships between variables. Patient-specific values were plotted on the corresponding axes for each variable. The scores for each variable were determined by drawing lines upward to the point scale, which corresponded to a predicted probability or response. Clinicians can predict an outcome by mapping patient values onto a chart and summing the points across all variables.

A receiver operating characteristic (ROC) curve, calibration curve, Hosmer–Lemeshow (H-L) test, and decision curve analysis (DCA) were used to evaluate the nomogram model in the training set. Internal validation was conducted using 1000 bootstrap resamplings. It was performed by resampling the dataset with replacement 1000 times. For each bootstrap sample, we refit the model and then tested its performance on the bootstrap sample. We computed the proportion of correct predictions (both true positives and true negatives) out of the total number of predictions to calculate accuracy. This gives a general measure of how well the model classifies outcomes. The Kappa statistic was calculated to measure the agreement between predicted and observed outcomes while accounting for agreement occurring by chance. An area under curve (AUC) of 0.5 to 0.7 signified low predictive value, 0.7 to 0.9 signified moderate predictive value, and >0.9 signified high predictive value.[20]

Establishment of a scoring model in the training cohort

To convert continuous variables to dichotomous variables, a cut-off point was selected based on ROC curves, and the threshold values of these variables were rounded off by clinical practice and convenience. The weight of each variable was determined by the coefficient values of each variable from the binary logistic regression analysis. Total score of each patient was calculated by summing the scores of the variables. Furthermore, using a ROC curve to evaluate the diagnostic capability of the model, from which the cut-off value was determined by the maximum Youden index.

Variables	Responders (n = 173)	Non-responders (n = 145)	t/Z/χ2 value	P value
Demographic variables				
Age (year)	12.0 (11.0, 13.0)	12.0 (10.0, 13.0)	−0.810	0.117
Sex (M/F)	88/85	61/84	2.452	0.406
Weight (kg)	46.0 (37.4, 54.5)	44.0 (36.3, 54.8)	−0.653	0.514
Height (cm)	160.0 (146.5, 168.0)	157.0 (145.5, 165.0)	−1.166	0.244
Medical history				
Family history (Y/N)	27/146	12/133	3.940	0.047
Course (month)	6 (1, 24)	8 (2, 24)	0.615	0.538
Pre-treatment SS	1 (1, 3)	1 (1, 2)	−1.248	0.212
Post-treatment SS	0 (0, 0)	1 (1, 2)	−14.480	<0.001

SS, symptom score; Y/N, have symptoms or no symptoms.

Table 1: **Demographic and medical history variables between responders and non-responders to metoprolol in children with vasovagal syncope in the training cohort.**

External validation of the predicting models

We calculated the C-index value and plotted a ROC curve in the validation cohort to validate the nomogram model. A C-index of 0.7–0.8 indicated that the model had generally considered acceptable discrimination, 0.8–0.9 indicated very good discriminatory power, and >0.9 indicated an outstanding discriminatory ability.[21] To verify the prediction efficiency of the scoring system model, the total score of children with VVS in the external validation cohort was also calculated. The predicted outcomes were then compared with the actual clinical treatment effects to calculate sensitivity, specificity, and accuracy. H-L test was performed to assess the goodness-of-fit of the scoring model in the validation cohort.

Variables	Responders (n = 173)	Non-responders (n = 145)	t/Z/χ2 value	P value
Triggers of syncope				
Prolonged standing (Y/N)	76/97	90/55	10.401	0.001
Postural changes (Y/N)	56/117	60/85	2.763	0.096
Anxious (Y/N)	10/163	10/135	0.167	0.683
Sweltering environment (Y/N)	14/159	15/130	0.483	0.487
Symptoms of pre-syncope				
Dizziness (Y/N)	116/57	107/38	1.711	0.191
Headache (Y/N)	25/148	22/123	0.033	0.857
Dark vision (Y/N)	63/110	79/66	10.418	0.001
Blurred vision (Y/N)	35/138	33/112	0.300	0.584
Chest tightness (Y/N)	59/114	38/107	2.321	0.128
Palpitation (Y/N)	18/155	16/129	0.033	0.856
Nausea or vomiting (Y/N)	29/144	22/123	0.148	0.700
Abdominal pain (Y/N)	14/159	9/136	0.418	0.518
Sweating (Y/N)	38/135	40/105	1.346	0.246
Pale complexion (Y/N)	52/121	60/85	4.432	0.035
Fatigued (Y/N)	34/139	38/107	1.934	0.164
Tinnitus (Y/N)	4/169	12/133	5.872	0.015
Symptoms after syncope				
Dizziness (Y/N)	14/159	17/128	1.183	0.277
Headache (Y/N)	9/164	9/136	0.149	0.699
Fatigued (Y/N)	33/140	17/128	3.217	0.073
Confused consciousness (Y/N)	1/172	0/145	0.841	0.359

Y/N, have symptoms or no symptoms.

Table 2: **Triggers and symptoms of syncope between responders and non-responders to metoprolol in children with vasovagal syncope in the training cohort.**

Ethics

The study was conducted in compliance with the ethical standards described in the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Peking University First Hospital, China (Approval No. 2022 [382–002]). Ethical approval was also granted by the Ethics Committee of the Children's Hospital, Capital Institute of Paediatrics (Approval No. SHERLL2022063) and the Second Xiangya Hospital, Central South University (Approval No. 2022 [249]). All participants and their legal guardians provided informed consent.

Statistical analysis

Data were analysed with SPSS statistics (version 25.0) and R (version 4.1.2). Statistical significance was set at $P < 0.05$.

Univariate analysis

Normally distributed continuous variables are presented as mean ± standard deviation, while non-normally distributed variables are shown as median (25th and 75th percentiles) according to the Shapiro–Wilk test. Categorical variables are expressed as the number of cases. We employed multiple imputation using chained equations (MICE) to handle missing continuous data. The independent samples t-test or Mann–Whitney U-test was used for intergroup comparisons of continuous variables and the Chi-square test was used for categorical variables.

Multivariate regression analysis

Following the univariate analysis of the training cohort, factors showing significant differences ($P < 0.05$) between the responders and non-responders to paediatric patients with VVS were conducted the collinearity analysis. A linear regression model was used to analyse the collinearity between the variables. Collinearity severity was quantified using the variance inflation factor (VIF) and the tolerance value, with thresholds set at VIF< 10 and tolerance >0.1, indicating acceptable levels of collinearity. Variables meeting these criteria were subsequently included in a binary logistic regression model using a backward stepwise regression approach, using treatment efficacy grouping as the dependent variable. Variables were iteratively removed from the model based on their lack of predictive power, using likelihood-ratio tests to determine each variable's contribution to the model. Variables with a P value greater than 0.05 were removed from the model during

the selection process. The remained variables demonstrated statistical significance, low multicollinearity, and strong predictive value in the final logistic regression model to predict the therapeutic effect of metoprolol.

Role of the funders
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Comparison baseline characteristics between responders and non-responders
Compared with non-responders, patients in the metoprolol responder group were less prone to syncope induced by prolonged standing. Pre-syncopal symptoms, such as vision darkening, pallor, and tinnitus, were less common among metoprolol responders. Patients in the metoprolol responder group had longer positive response times and a higher increased HR during a positive response in HUTT (ΔHR). Responders had a lower Pmax, Pmin, Pcmin, QTmin, and SDNN, as well as a longer QTmax, QTcmax, QTd, and QTcd than non-responders (all $P < 0.05$) (Tables 1–4).

Variables	Responders (n = 173)	Non-responders (n = 145)	*t/Z/χ2 value*	P value
Hemodynamic type				
Vasoinhibitory type	135	105	1.354	0.508
Cardioinhibitory type	12	13		
Mixed type	26	27		
Time from supine to positive response in HUTT (min)	35 (18, 48)	33 (18, 35)	−2.258	0.024
Supine HR (bpm)	76 (69, 83)	76 (68, 83)	−0.010	0.992
Supine SBP (mmHg)	109 (103, 119)	107 (101, 115)	−1.852	0.064
Supine DBP (mmHg)	64 (59, 69)	64 (59, 67)	−1.824	0.068
ΔHR (bpm)	54 (42, 66)	38 (26, 46)	−7.991	<0.001

HUTT, head-up tilt test; ΔHR, increased HR during positive response in HUTT.

Table 3: **Variables in head-up tilt test between responders and non-responders to metoprolol in children with vasovagal syncope in the training cohort.**

ΔHR, QTcd, and SDNN were effective predictors of metoprolol treatment efficacy in children with VVS
Among the 15 abovementioned parameters in Tables 1–4, 12 indicators were selected to develop

Variables	Responders (n = 173)	Non-responders (n = 145)	*t/Z/χ2 value*	P value
Electrocardiogram variables				
Pmax (ms)	95 (83, 104)	102 (84, 115)	−3.001	0.003
Pmin (ms)	60 (53, 72)	70 (60, 80)	−4.274	<0.001
Pcmax (ms)	106.61 (92.22, 121.11)	113.59 (92.82, 128.19)	−1.832	0.067
Pcmin (ms)	69.19 (59.43, 81.03)	77.21 (64.53, 89.74)	−3.459	0.001
Pd (ms)	31.0 (20.0, 40.0)	30.0 (20.0, 40.0)	−0.408	0.683
Pcd (ms)	35.49 (24.59, 44.50)	34.21 (24.49, 43.94)	−0.871	0.384
QTmax (ms)	391.0 (371.0, 412.0)	382.0 (367.36, 404.0)	−2.104	0.005
QTmin (ms)	350.0 (333.0, 368.0)	360.0 (340.0, 378.0)	−2.816	0.005
QTcmax (ms)	444.24 (424.25, 467.08)	430.0 (411.05, 446.25)	−4.563	<0.001
QTcmin (ms)	396.16 (377.0, 414.25)	398.0 (385.67, 414.05)	−0.853	0.394
QTd (ms)	40.0 (30.0, 56.0)	27.72 (13.5, 36.0)	−7.674	<0.001
QTcd (ms)	46.76 (34.64, 62.28)	29.64 (15.53, 39.12)	−7.932	<0.001
P wave amplitude (mV)	0.11 (0.09, 0.14)	0.10 (0.09, 0.12)	−1.053	0.292
Time domain indicators of Holter				
SDNN (ms)	139.0 (122.0, 165.6)	164.0 (133.5, 188.8)	−4.068	<0.001
SDANN (ms)	120.0 (106.0, 152.0)	134.4 (113.5, 156.8)	−1.804	0.071
rMSSD (ms)	60.0 (42.0, 82.8)	64.0 (50.0, 105.8)	−1.547	0.122
PNN50 (%)	23.7 (15.0, 35.8)	28.0 (16.0, 40.2)	−1.868	0.062
Echocardiography indicators				
LVEF (%)	69.6 (66.0, 74.0)	71.0 (67.3, 74.0)	−1.463	0.143
LVFS (%)	39.0 (36.0, 43.0)	40.0 (37.0, 43.0)	−1.425	0.154

LEVF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; NN, normal to normal heartbeat; Pcd, corrected P-wave dispersion; Pcmax, corrected maximum P-wave duration; Pcmin, corrected minimum P-wave duration; Pd, P-wave dispersion; Pmax, maximum P-wave duration in 12-lead electrocardiogram; Pmin, minimum P-wave duration in 12-lead electrocardiogram; PNN50, the percentage of successive NN intervals that differ by more than 50 ms; QTcd, corrected QT interval dispersion; QTcmax, corrected maximum QT interval; QTcmin, corrected minimum QT interval; QTd, QT interval dispersion; QTmax, maximum QT interval in 12-lead electrocardiogram; QTmin, minimum QT interval in 12-lead electrocardiogram; rMSSD, the root mean square of successive differences; SDNN, the standard deviation of all NN intervals; SNANN, the standard deviation of the average NN interval for all 5-min segments in the entire recording.

Table 4: **Electrocardiogram, Holter, and Echocardiography Parameters between responders and non-responders to metoprolol in children with vasovagal syncope in the training cohort.**

Variables	Tolerance	VIF
Syncope Trigger of prolonged standing	0.785	1.273
Pre-syncope symptoms of dark vision	0.870	1.149
Pre-syncope symptoms of pale complexion	0.891	1.122
Pre-syncope symptoms of tinnitus	0.955	1.047
Time from supine to positive response in HUTT (min)	0.757	1.321
ΔHR (bpm)	0.845	1.183
Pmax (ms)	0.444	2.251
Pcmin (ms)	0.365	2.742
QTmin (ms)	0.383	2.608
QTcmax (ms)	0.360	2.775
QTcd (ms)	0.292	3.426
SDNN (ms)	0.822	1.216

HUTT, head-up tilt test; ΔHR, increased HR during positive response in HUTT; Pmax, maximum P-wave duration in 12-lead electrocardiogram; Pcmin, corrected minimum P-wave duration in 12-lead electrocardiogram; QTcd, corrected QT dispersion; QTcmax, corrected maximum QT interval; QTmax, maximum QT interval in 12-lead electrocardiogram; SDNN, the standard deviation of all NN intervals; VIF, variance inflation factor.

Table 5: **Collinearity analysis of the 12 indicators included after univariate analysis in training cohort.**

prediction model based on results of collinearity analysis and clinical relevance, including trigger of prolonged standing, pre-syncope symptoms of vision darkening, pallor, and tinnitus, positive response time and ΔHR in HUTT, pre-treatment Pmax, Pcmin, QTmin, QTcmax, QTcd, and SDNN (Table 5 and Supplementary Table S1). Using the binary logistic regression, we developed a regression equation to predict the effect of metoprolol in paediatric VVS as shown below (Table 6):

$$\text{Logit}(P) = -3.053 + 0.099 \times \Delta HR + 0.069 \times QTcd - 0.034 \times SDNN.$$

The predictive model was adjusted for varying covariates (age, sex, weight, height, and the duration of medication use). The results showed a good consistency across models (Table 7).

Variables	Coefficient	SE	Wald	P value	OR	95% CI
ΔHR (bpm)	0.099	0.013	58.696	<0.01	1.104	1.076–1.132
QTcd (ms)	0.069	0.010	44.814	<0.01	1.071	1.050–1.093
SDNN (ms)	−0.034	0.005	40.664	<0.01	0.967	0.957–0.977
Constant	−3.053	1.050	8.453	0.004	0.047	

The predictive model was constructed to predict the treatment efficacy of metoprolol in children with vasovagal syncope. The logistic regression equation was as follows: Logit (P) = −3.053 + 0.099 × ΔHR + 0.069 × QTcd–0.034 × SDNN. ΔHR, increased HR during positive response in HUTT; QTcd, corrected QT interval dispersion; SDNN, the standard deviation of all NN intervals.

Table 6: **Multivariable logistic regression analysis of therapeutic response to metoprolol in children with vasovagal syncope in training cohort.**

Development and evaluation of the nomogram model in the training cohort

The predictive model containing baseline ΔHR, QTcd, and SDNN was developed and presented as the nomogram (Fig. 2). The AUC of ROC curve was 0.900 (95% CI: 0.867–0.932) in the training cohort (Fig. 3A). A calibration curve for the nomogram in training cohort showed a strong alignment between the calibration and standard curves (Fig. 3B). The H-L test demonstrated a strong consistency between the prediction model and the observed outcomes ($\chi 2$ = 7.242, P = 0.511). The DCA demonstrated that using the nomogram model can significantly enhance clinical benefits (Fig. 3C). Internal validation showed that the predictive model had a good predictive value with an accuracy of 0.806 and a kappa value of 0.608.

Validation of the nomogram model in the external validation cohort

In the external validation cohort, the C-index of the nomogram model was 0.81, indicating that it had a very good discriminatory power and the AUC was 0.784 (95% CI: 0.705–0.863) (Fig. 3D).

Development and evaluation of the scoring model in the training cohort

The AUCs of the ΔHR, QTcd, and SDNN to predict the metoprolol efficacy were 0.758, 0.632, and 0.760, respectively. The cut-off values for prediction were 47.5 bpm, 40.66 ms, and 154.2 ms, respectively. The sensitivities were 69.9%, 71.7%, and 60.7%, whereas the specificities were 82.8%, 80.0%, and 30.6%, respectively (Fig. 4A).

We defined 3 points for ΔHR ≥48 bpm and 0 points for ΔHR <48 bpm, 2 points for QTcd ≥40.66 ms and 0 points for QTcd <40.66 ms, and 1 point for SDNN ≤154 ms and 0 points for SDNN >154 ms (Table 8). The ROC curve analysis identified a cut-off value of 2.5 points, with a remarkably high AUC of 0.941 (95% CI: 0.897–0.985). The model showed a sensitivity of 82.8%, a specificity of 96.5%, and an accuracy of 89.94% to predict good therapeutic effect of metoprolol (Fig. 4B and C, and Supplementary Table S2). The H-L test showed that model fits the data well in training cohort ($\chi 2$ = 11.259, P = 0.187).

Validation of the scoring model in the external validation cohort

The scoring model showed an AUC of was 0.859 (95% CI: 0.789–0.927) in the validation cohort. Using a total score threshold of ≥2.5 to predict the effective of metoprolol treatment, the scoring system demonstrated a sensitivity of 93.6%, a specificity of 80.9%, and an accuracy of 87.7% (Table 9). The H-L test showed that model fits the data well in validation cohort ($\chi 2$ = 10.722, P = 0.218).

Variables	Model 1		Model 2		Model 3	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
ΔHR (bpm)	1.104 (1.074–1.134)	P < 0.01	1.110 (1.080–1.140)	P < 0.01	1.106 (1.076–1.137)	P < 0.01
QTcd (ms)	1.067 (1.036–1.098)	P < 0.01	1.072 (1.041–1.103)	P < 0.01	1.070 (1.038–1.102)	P < 0.01
SDNN (ms)	0.964 (0.953–0.976)	P < 0.01	0.966 (0.955–0.977)	P < 0.01	0.965 (0.953–0.976)	P < 0.01

Model 1 was adjusted for age, sex, weight, and height; Model 2 was adjusted for the duration of medication use; Model 3 was further adjusted for the duration of medication use, building upon the adjustments made in Model 1.

Table 7: **Adjusted ORs and 95%CIs of the multivariable logistic regression of therapeutic response to metoprolol in children with vasovagal syncope in training cohort.**

Discussion

Our study revealed that the pre-treatment ΔHR, QTcd, and SDNN can serve as reliable predictors of metoprolol efficacy for managing children with VVS. Using these three indicators, a nomogram to predict the effectiveness of metoprolol in paediatric VVS was established with an AUC of 0.900 (95% CI: 0.867–0.932). The nomogram model in external validation cohort also demonstrated very good discriminatory power. A predictive scoring model was established by calculating the corresponding scores based on the regression coefficients β of each variable. It offers quick decision-making support without the need for complex calculations, making it more accessible for healthcare professionals in daily practice. In training cohort, a total score ≥2.5 demonstrated a sensitivity of 82.8% and a specificity of 96.5% in predicting the therapeutic efficacy of metoprolol in VVS patients. In the validation cohort, when the total score of the patient was ≥2.5, the sensitivity, specificity, and accuracy were 93.6%, 80.9%, and 87.7%, respectively.

Overactivation of sympathetic nervous system is one of the primary pathophysiological mechanisms underlying VVS in children.[22] When transitioning from a supine to an upright position, there is an immediate gravitational shift of blood volume towards the abdomen and lower limbs. This rapid redistribution triggers a baroreflex response as arterial blood pressure decreases, prompting baroreceptors to send fewer impulses to the central nervous system.[23] This causes a reduction in

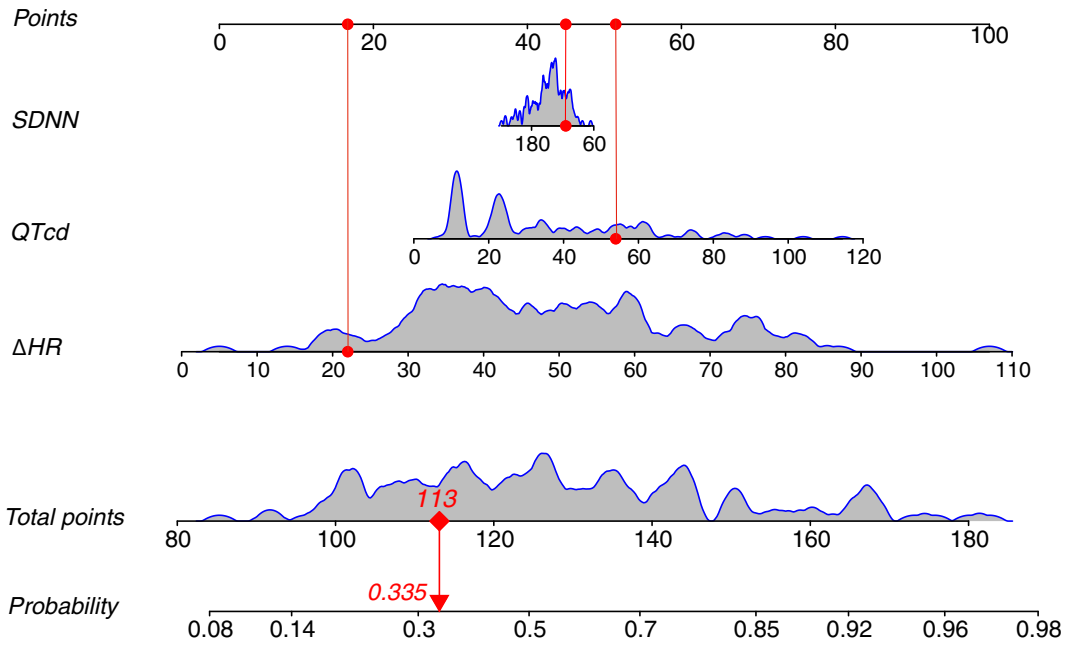

Fig. 2: **Nomogram for predicting the efficacy of metoprolol in children with vasovagal syncope in the training cohort.** For example, if a child has a SDNN of 113 ms, a QTcd of 53.93 ms, and a ΔHR of 22 bpm, the corresponding scores, which are marked with red dots on the top horizontal line, can be acquired. Therefore, the total number of points is approximately 113. A dot representing the total number of points corresponds to a probability of 0.335, which is marked by the red arrow on the bottom horizontal line. Thus, metoprolol is not recommended for use. ΔHR, increased HR during positive response in HUTT; QTcd, the corrected QT interval dispersion; SDNN, the standard deviation of all NN intervals.

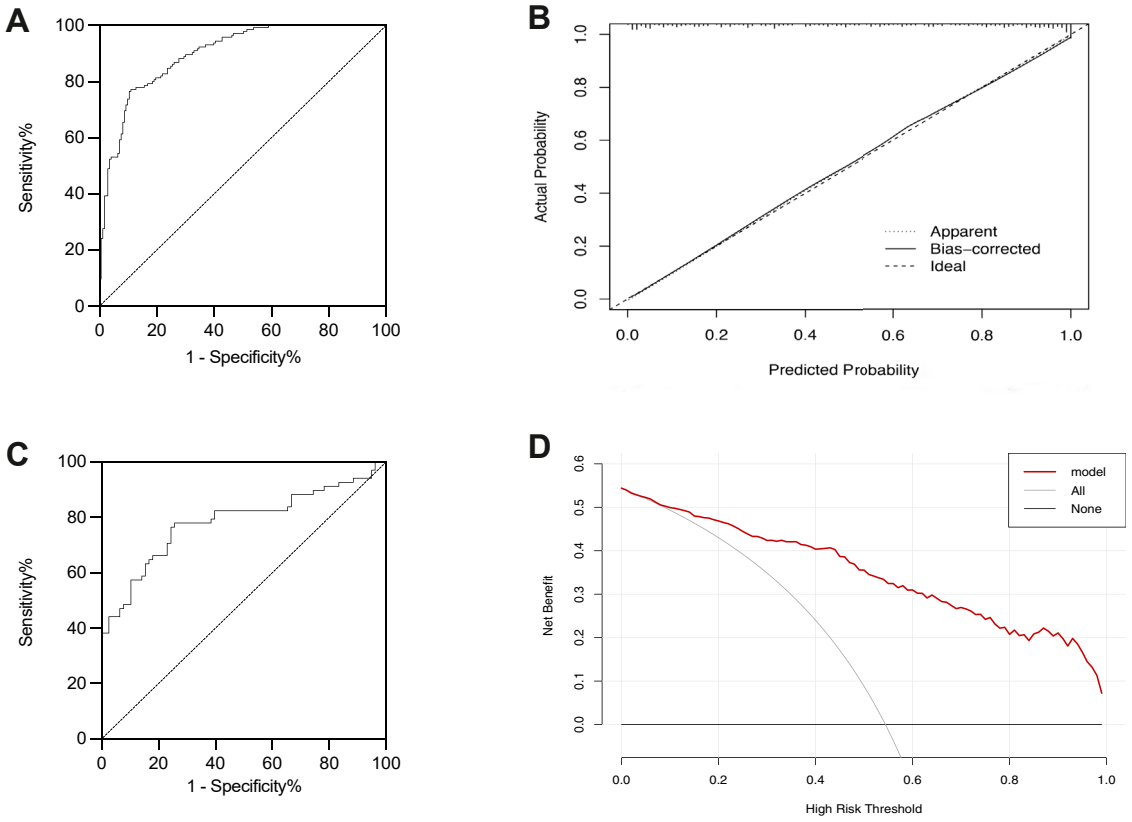

Fig. 3: **Evaluation and validation of nomogram model for evaluating the effectiveness of metoprolol in children with vasovagal syncope.** (A) ROC curve of the nomogram model in the training cohort. The AUC in training cohort was 0.900 (95% CI: 0.867–0.932). (B) Calibration curve of the nomogram model in the training cohort; The x-axis shows the predicted probability of the metoprolol response, and the y-axis shows the observed probability of the metoprolol response. The ideal line means that the predicted and actual probabilities of the model agree perfectly. The apparent line indicates the actual performance of the prediction model in the training cohort. The bias-corrected line indicates the performance of the prediction model in the training cohort after the correction of the overfitting situation. The calibration curve and standard curve have a good fit in training cohort. (C) ROC curve of the nomogram model in the validation cohort. The AUC in the validation cohort was 0.784 (95% CI: 0.705–0.863). (D) DCA curve of the nomogram model in the training cohort; The x-axis displays the probability threshold. The y-axis indicates the degree of benefit to which the patient benefited from the intervention of metoprolol. AUC, the area under curve; DCA, decision curve analysis. ROC, receive operator curve.

parasympathetic nerve tension and an enhancement in sympathetic nerve activity, leading to increased HR and myocardial contractility. The increased sympathetic activity leads to enhanced ventricular contraction, which is detected by inhibitory mechanoreceptors in the left ventricular wall, which subsequently activate high-pressure C-fibres. This activation of high-pressure C-fibre afferents results in central paradoxical vagal excitement, manifested as reflexive bradycardia, vasodilation, and hypotension, a phenomenon termed the Bezold–Jarisch reflex.[23] Therefore, the increase in heart rate before a positive response in the HUTT for patients with VVS can effectively reflect the excitability of the sympathetic nervous system, helping us predict the treatment outcome of metoprolol. Leor et al.[24] observed that adults with VVS who experienced significant tachycardia before fainting during the HUTT were more likely to benefit from β-blocker therapy.

The ECG provides a snapshot of the electrophysiological activity within cardiac myocytes. The autonomic nervous system modulates this activity by modulating neural impulses and neurotransmitter release, thereby influencing the depolarization and repolarisation of the myocardium.[25,26] The QT interval is a measurement on an ECG that represents the time span from the beginning of ventricular depolarisation (when the heart's ventricles contract) to the end of ventricular repolarization (when the ventricles return to their resting state). It reflects the total time taken for the ventricles to undergo a full cycle of contraction and relaxation.[27] QTcd compensates for the HR variation and is modulated by the autonomic nervous system.[28] Increased QTcd

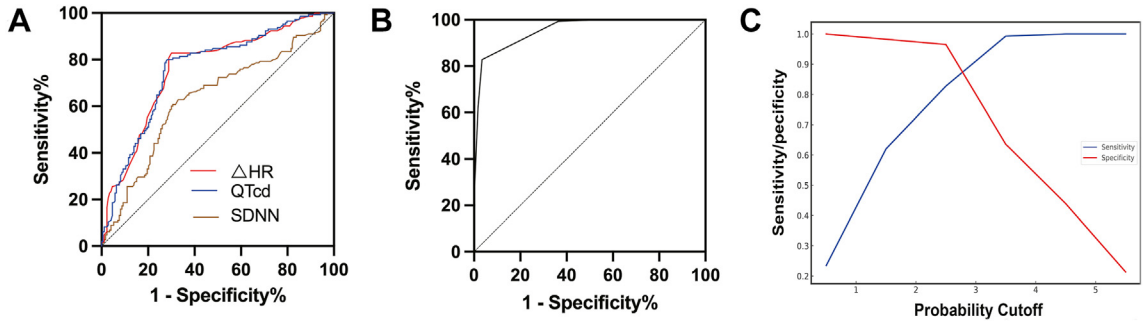

Fig. 4: **ROC curve of the indicators and scoring model for evaluating the effectiveness of metoprolol in children with vasovagal syncope in the training cohort.** (A) ROC curves of indicators. ROC analysis revealed that the ΔHR, QTcd, and SDNN in logistic regression model were predictors of metoprolol efficacy, with AUCs of 0.760 (95% CI: 0.707–0.814), 0.758 (95% CI: 0.705–0.812), and 0.632 (95% CI: 0.570–0.695), respectively. The optimal cutoff values were 48 bpm, 40.66 ms, and 154 ms, respectively. The sensitivity for predicting metoprolol efficacy in VVS children was 69.9%, 71.7%, and 60.7%, while the specificity was 82.8%, 80.0%, and 30.6%, respectively. (B) ROC curve of scoring model. The ROC curve revealed a cutoff value of 2.5 points with an AUC of 0.941 (95% CI: 0.897–0.985). When the score was ≥2.5 points, the sensitivity of this scoring model was 96.5% and the specificity was 82.8%. (C) Optimal cut-off point identification by Youden method to discriminate between responders and non-responders to metoprolol treatment. AUC, the area under curve; ΔHR, increased HR during positive response in HUTT compared with baseline value; QTcd, the corrected QT interval dispersion; ROC, receive operator curve; SDNN, the standard deviation of all NN intervals.

suggests greater variability in the repolarization times of different parts of the ventricles, which can be a marker for an increased risk of cardiac events. While there may be some debate regarding the role of QTc in predicting prognosis, it still holds significant value in assessing autonomic nervous system function. It was reported that QTc interval prolongation could serve as an important marker for autonomic dysfunction, including in conditions like diabetic autonomic neuropathy[29] and long QT syndrome[30] in children. The QTd in children with VVS was significantly larger than that in healthy children, indicating that these patients with VVS had autonomic dysfunction.[31] In our study, we observed that children in the responder group had greater QTd and QTcd values than those in the non-responder group. This suggests that patients with VVS in the effective treatment group may have an elevated sympathetic nervous system activity before treatment. As a measurement indicator, QTcd may exhibit variability in both interobserver and intra-subject measurements, which can to a certain extent compromise its reliability and clinical utility.[32,33] To minimize potential errors, we have implemented standardized operating procedures for the measurement of QTcd (Supplementary Table S3). Further studies are also needed to validate the predictive role of QTcd in VVS and other cardiovascular diseases.

Our study found that children with reduced SDNN showed better responses to metoprolol treatment. The SDNN is an important time–domain parameter typically utilised for analysing HRV, representing the variability in time intervals between consecutive normal heartbeats. HRV represents the overall manifestation of all changes in instantaneous HR.[34] The SDNN represents the overall HRV throughout the day, and a decreased SDNN generally indicates an imbalance in autonomic nervous function, characterized by higher sympathetic nervous activity or lower parasympathetic activity.[35,36] Consequently, children with lower SDNN levels may inherently have higher sympathetic nervous system tension, making them more likely to benefit from metoprolol treatment, which inhibits sympathetic nervous system activity.

Currently, there is no gold-standard evidence available, and only a few small-sample predictive studies from our research group exist. Previous studies on predicting the therapeutic effect of metoprolol for VVS in paediatric patients have employed biomarkers, such as baroreflex sensitivity assessed during the HUTT.[37]

Variables	Cut off value	Variable assignments	Coefficient	Score
ΔHR	48 bpm	"ΔHR ≥ 48 bpm" = 3, "ΔHR < 48 bpm" = 0	0.099	3
QTcd	40.66 ms	"QTcd ≥40.66 ms" = 2, "QTcd <40.66 ms" = 0	0.069	2
SDNN	154 ms	"SDNN ≤154 ms" = 1, "SDNN >154 ms" = 0	−0.034	1

ΔHR, increased HR during positive response in HUTT; QTcd, corrected QT interval dispersion; SDNN, the standard deviation of all NN intervals.

Table 8: **Coefficients of binary regression model and variables assignments in predictive scoring model of metoprolol for children with vasovagal syncope in training cohort.**

Scoring model-predicted efficacy outcome	Clinical standard-based followed-up efficacy outcome		Total
	Number of responders	Number of non-responders	
Number of patients with predictive score ≥2.5	73	13	86
Number of patients with predictive score <2.5	5	55	60
Total	78	68	146

Table 9: **Predictive values of scoring model of predictive scoring model of metoprolol for children with vasovagal syncope in external validation cohort.**

However, obtaining baroreflex sensitivity readings relies on specialized equipment, which is difficult for primary care hospitals to access and apply. Moreover, Poincaré plots require image processing software to measure the longitudinal and transverse axes, and the data extraction process can be complex.[38] For the 24-h urine norepinephrine measurement, high-performance liquid chromatography is required, which is complex.[39] Additionally, the collection and storage of a 24-h urine sample can be cumbersome. In contrast, the indicators used in this study offer a non-invasive, rapid, simple, and cost-effective measurement method. Furthermore, the predictive model developed in the present study integrates a multitude of indicators and factors, and has achieved very good predictive results with high specificity and sensitivity.

It is notable that the inconsistency regarding the predictive value of LVEF and LVFS between our current findings and previous publications.[29] It can likely be attributed to several factors. First, the differences in study populations could account for the variability, as inclusion criteria, baseline characteristics, or disease severity across the study cohorts. Second, although echocardiography is a simple and non-invasive procedure, it does carry a certain degree variability among different operators. Third, sample size and statistical power may also play a role. Lastly, it is important to consider the potential influence of other variables in the multivariate analysis, which may have overshadowed the predictive value of LVEF and LVFS in our current model.

Our study had some limitations. As our model was based on a retrospective cohort, there may have been some inherent retrospective bias. The validation specificity of 80.9% and accuracy of 87.7% are relatively low for consideration in a clinical setting. For this issue, we will try to extend the follow-up duration and design further prospective validation studies to help refine the model in the future. Medications for treating VVS include agents such as midodrine hydrochloride and fludrocortisone besides of metoprolol. Future work should further explore individualized pharmacotherapy to enhance the management and treatment outcomes for pediatric patients with VVS.

Overall, our study was the first to develop and validate predictive models for the efficacy of metoprolol in treating pediatric VVS. The nomogram and scoring model we developed in the present study may assist clinicians in predicting and selecting treatment options, thereby individualising therapeutic regimens for children with VVS. This contribution was particularly significant given the variability in response to metoprolol and the limited guidance currently available for its use in pediatric populations.

Contributors

All authors have full access to all the data in the study and accept responsibility to submit for publication. The authors' contributions are as follows: Yaxi Cui, Jing Zhang, and Yuwen Wang, Ying Liao had primary responsibility for the protocol development, patient enrolment, data collection and verification, preliminary data analysis, and writing of the draft. Keyu Liu, Wenrui Xu, Shu Wu, Chufan Sun, Chunyu Zhang, Qingyou Zhang, Ping Liu, Yuli Wang, Yanjun Deng, Chen Shen, Yao Lin, Hong Cai, Juan Zhang, Runmei Zou, Ping Liu, and Shuo Wang gave important advice on the study design, collected data, and reviewed the manuscript for important intellectual content. Junbao Du, Hongfang Jin, Lin Shi, and Cheng Wang supervised the design and execution of the study, checked the data analysis, contributed to the writing of the manuscript, and had final approval of the manuscript submitted. All the authors have read and approved the final version of the manuscript.

Data sharing statement

Any data not published within the article will be shared in an anonymised format by request from any qualified investigator. If desired, please contact the corresponding author of this article.

Declaration of interests

All authors declare no conflicts of interest.

Acknowledgements

This research was funded by National High-Level Hospital Clinical Research Funding (Clinical Research Project of Peking University First Hospital, grant number 2022CR59).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105595.

References

1 Kanjwal K, Calkins H. Syncope in children and adolescents. *Cardiol Clin*. 2015;33(3):397–409.
2 Brignole M, Moya A, de Lange FJ, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39(21):1883–1948.
3 Kenny RA, McNicholas T. The management of vasovagal syncope. *QJM*. 2016;109(12):767–773.
4 Serletis A, Rose S, Sheldon AG, Sheldon RS. Vasovagal syncope in medical students and their first-degree relatives. *Eur Heart J*. 2006;27(16):1965–1970.
5 Tao C, Cui Y, Zhang C, et al. Clinical efficacy of empirical therapy in children with vasovagal syncope. *Children*. 2022;9(7):1065.
6 Kruit MC, Thijs RD, Ferrari MD, Launer LJ, van Buchem MA, van Dijk JG. Syncope and orthostatic intolerance increase risk of brain lesions in migraineurs and controls. *Neurology*. 2013;80(21):1958–1965.
7 Sanatani S, Chau V, Fournier A, Dixon A, Blondin R, Sheldon RS. Canadian cardiovascular society and Canadian pediatric cardiology association position statement on the approach to syncope in the pediatric patient. *Canadian J cardio*. 2017;33(2):189–198.
8 Wang C, Li Y, Liao Y, et al. 2018 Chinese pediatric cardiology society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents. *Sci Bull*. 2018;63(23):1558–1564.
9 Zhang Q, Jin H, Wang L, Chen J, Tang C, Du J. Randomized comparison of metoprolol versus conventional treatment in preventing recurrence of vasovagal syncope in children and adolescents. *Med Sci Monit*. 2008;14(4):CR199–CR203.
10 Hatoum T, Raj S, Sheldon RS. Current approach to the treatment of vasovagal syncope in adults. *Intern Emerg Med*. 2023;18(1):23–30.
11 Song J, Li H, Wang Y, et al. Left ventricular ejection fraction and fractional shortening are useful for the prediction of the therapeutic response to metoprolol in children with vasovagal syncope. *Pediatr Cardiol*. 2018;39(7):1366–1372.
12 Wang Y, Sun Y, Zhang Q, et al. Baseline corrected QT interval dispersion is useful to predict effectiveness of metoprolol on pediatric postural tachycardia syndrome. *Front Cardiovasc Med*. 2021;8:808512.
13 Wang Y, Zhang C, Chen S, et al. Heart rate variability predicts therapeutic response to metoprolol in children with postural tachycardia syndrome. *Front Neurosci*. 2019;13:1214.

14 Reichlin T, Abächerli R, Twerenbold R, et al. Advanced ECG in 2016: is there more than just a tracing? *Swiss Med Wkly*. 2016;146:w14303.
15 Uberoi A, Jain NA, Perez M, et al. Early repolarization in an ambulatory clinical population. *Circulation*. 2011;124(20):2208–2214.
16 Cheema AN, Ahmed MW, Kadish AH, Goldberger JJ. Effects of autonomic stimulation and blockade on signal-averaged P wave duration. *J Am Coll Cardiol*. 1995;26(2):497–502.
17 Imamoglu EY, Oztunc F, Eroglu AG, Onal H, Guzeltas A. Dispersion of the P wave as a test for cardiac autonomic function in diabetic children. *Cardiol Young*. 2008;18(6):581–585.
18 Smith AH, Norris KJ, Roden DM, Kannankeril PJ. Autonomic tone attenuates drug-induced QT prolongation. *J Cardiovasc Electrophysiol*. 2007;18(9):960–964.
19 Winker R, Barth A, Dorner W, et al. Diagnostic management of orthostatic intolerance in the workplace. *Int Arch Occup Environ Health*. 2003;76(2):143–150.
20 Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied logistic regression*. John Wiley & Sons; 2013.
21 Harrell FE. Regression modeling strategies. New York: Springer; 2012.
22 Li H-X, Gao L, Yuan Y. Advance in the understanding of vasovagal syncope in children and adolescents. *World J Pediatr*. 2021;17(1):58–62.
23 Cui Y-X, Du J-B, Jin H-F. Baroreflex sensitivity and its implication in neurally mediated syncope in children. *World J Pediatr*. 2023;19(11):1023–1029.
24 Leor J, Rotstein Z, Vered Z, Kaplinsky E, Truman S, Eldar M. Absence of tachycardia during tilt test predicts failure of beta-blocker therapy in patients with neurocardiogenic syncope. *Am Heart J*. 1994;127(6):1539–1543.
25 Novak P. Autonomic disorders. *Am J Med*. 2019;132(4):420–436.
26 Rosenberg AA, Weiser-Bitoun I, Billman GE, Yaniv Y. Signatures of the autonomic nervous system and the heart's pacemaker cells in canine electrocardiograms and their applications to humans. *Sci Rep*. 2020;10(1):9971.
27 Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV. *Circulation*. 2009;119(10):e241–e250.
28 Vink AS, Neumann B, Lieve KVV, et al. Determination and interpretation of the QT interval. *Circulation*. 2018;138(21):2345–2358.
29 Takebayashi K, Aso Y, Sugita R, Takemura Y, Inukai T. Clinical usefulness of corrected QT intervals in diabetic autonomic neuropathy in patients with type 2 diabetes. *Diabete Metab*. 2002;28(2):127–132.
30 Yoshinaga M, Kucho Y, Ushinohama H, Ishikawa Y, Ohno S, Ogata H. Autonomic function and QT interval during nighttime sleep in infant long QT syndrome. *Circ J*. 2018;82(8):2152–2159.
31 Krasemann T, Strompen C, Blumenberg J, Gehrmann J, Burkhardtsmaier G, Vogt J. Changes of the corrected QT interval in healthy boys and girls over day and night. *Eur Heart J*. 2009;30(2):202–208.
32 Glancy JM, Weston PJ, Bhullar HK, Garratt CJ, Woods KL, de Bono DP. Reproducibility and automatic measurement of QT dispersion. *Eur Heart J*. 1996;17(7):1035–1039.
33 Alonso MAG, Lima VdACC, Carreira MAMdQ, Lugon JR. Reproducibility and reliability of QTc and QTcd measurements and their relationships with left ventricular hypertrophy in hemodialysis patients. *Arq Bras Cardiol*. 2017;109(3):222–230.
34 Grégoire J-M, Gilon C, Carlier S, Bersini H. Autonomic nervous system assessment using heart rate variability. *Acta Cardiol*. 2023;78(6):648–662.
35 Tiwari R, Kumar R, Malik S, Raj T, Kumar P. Analysis of heart rate variability and implication of different factors on heart rate variability. *Curr Cardiol Rev*. 2021;17(5):e160721189770.
36 Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health*. 2017;5:258.
37 Tao C, Li X, Tang C, Jin H, Du J. Baroreflex sensitivity predicts response to metoprolol in children with vasovagal syncope: a pilot study. *Front Neurosci*. 2019;13:1329.
38 Yuan P, Li X, Tao C, et al. Poincaré plot can be a useful tool to select potential responders to metoprolol therapy in children with vasovagal syncope. *Inter J Gen Med*. 2022;15:2681–2693.
39 Kong Q, Yang X, Cai Z, et al. Twenty-four-hour urine NE level as a predictor of the therapeutic response to metoprolol in children with recurrent vasovagal syncope. *Ir J Med Sci*. 2019;188(4):1279–1287.