RENAL FAILURE
2025, VOL. 47, NO. 1, 2478487
https://doi.org/10.1080/0886022X.2025.2478487

Taylor & Francis
Taylor & Francis Group

CLINICAL STUDY

OPEN ACCESS Check for updates

Prediction of intradialytic hypotension based on heart rate variability and skin sympathetic nerve activity using LASSO-enabled feature selection: a two-center study

Yike Zhang[a*], Shuang Su[b*], Zhenye Chen[a*], Yaoyu Huang[c], Yujun Qian[c], Chang Cui[a], Yantao Xing[d], Ningning Wang[c], Hongwu Chen[a], Huijuan Mao[c] and Jing Wang[c]

[a]Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China; [b]Department of Nephrology, Nanjing Pukou People's Hospital, Nanjing, China; [c]Department of Nephrology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China; [d]Intelligent Systems Engineering Department, Indiana University Bloomington, Bloomington, Indiana, USA

ABSTRACT

Background: Intradialytic hypotension (IDH) is a prevalent complication during hemodialysis (HD). However, conventional predictive models are imperfect due to multifaceted etiologies underlying IDH.

Methods: This study enrolled 201 patients undergoing maintenance HD across two centers. Seventy percent of the patient cohort was randomly allocated to the training cohort ($n=136$), while the remaining 30% formed the validation cohort ($n=65$). IDH was defined as a reduction in systolic blood pressure (SBP) ≥20 mmHg or mean arterial pressure (MAP) ≥10 mmHg. Clinical data and autonomic nervous parameters, including skin sympathetic nerve activity (SKNA) and heart rate variability (HRV) during the initial 30 min of HD, were employed to construct the model. The least absolute shrinkage and selection operator (LASSO) regression facilitated variable selection associated with IDH. Subsequently, a multivariable logistic regression model was formulated to predict the risk of IDH and establish the nomogram.

Results: Sixty-six baseline features were included in the LASSO-regression model. In the final multivariable logistic regression model, 5 variables (SBP_0, $aSKNA_0$, $\triangle aSKNA_{0\text{-}30}$, $SDNN_0$, $\triangle SDNN_{0\text{-}30}$) were incorporated into the nomogram. The AUC was 0.920 (95% CI, 0.878-0.962) in the training cohort and 0.855 (95% CI, 0.763-0.947) in the validation cohort, indicating concordance between the nomogram prediction and actual observation of IDH.

Conclusion: The LASSO-enabled model, based on clinical characteristics and autonomic nervous system parameters from the first 30 min of HD, shows promise in accurately predicting IDH.

ARTICLE HISTORY
Received 14 October 2024
Revised 7 February 2025
Accepted 4 March 2025

KEYWORDS
Hemodialysis; intradialytic hypotension; heart rate variability; skin sympathetic nerve activity; LASSO regression

1. Introduction

The prevalence of chronic kidney disease (CKD) has been steadily increasing in recent years. CKD can progress to end-stage kidney disease (ESKD), requiring renal replacement therapy such as hemodialysis (HD). Intradialytic hypotension (IDH) is one of the frequent and severe complications during HD. The incidence of IDH is about 8-40% [1,2], accompanied by uncomfortable symptoms, insufficient dialysis, vascular access failure, and adverse long-term outcomes, including increased cardiovascular and all-cause mortality [3–8]. The pathophysiology of IDH is complicated [9]; however, the main driver of IDH is fluid extraction by ultrafiltration during dialysis resulting in blood pressure instability.

The autonomic nervous system, which is highly sensitive to blood volume alterations, plays a crucial role in the development of IDH. Heart rate variability (HRV) is a noninvasive method to estimate ANS activity. In previous studies, lower levels or changes in HRV indices at the initiation of HD were indicators for IDH [10,11]. However, HRV has limitations in directly reflecting autonomic nerve activity and tracking real-time changes, which cannot reflect the adaptive capacity of the autonomic nervous system (ANS) under hypovolemic stress. Skin sympathetic nerve activity (SKNA), which is acquired by high-sampling rate using traditional ECG electrodes, can reflect the sympathetic nerve activity noninvasively [12,13]. This technique has been widely used to

CONTACT Huijuan Mao maohui.juan72@njmu.edu.cn; Jing Wang wangjing2012@njmu.edu.cn Department of Nephrology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China.
*Yike Zhang, Shuang Su and Zhenye Chen contributed equally to this work as first authors.

evaluate the autonomic nervous function in patients with obstructive sleep apnea [14,15], hemorrhage [16,17].

In this study, we conducted recordings of single-lead high-frequency ECG on patients during the initial 30 min of HD. By integrating the evaluation of autonomic activity, including HRV and SKNA, along with demographic data and laboratory records, the aim of the study was to develop a useful model to predict IDH.

2. Materials and methods

2.1. Definition of IDH

The definition of IDH in this study was based on European Best Practice Guideline (EBPG) on hemodynamic instability: A decrease in systolic blood pressure (SBP) ≥20 mmHg or in mean arterial pressure (MAP) ≥10 mmHg associated with a clinical event and the need for nursing intervention [18].

2.2. Study population

Patients undergoing maintenance HD were enrolled from Nanjing Pukou People's Hospital (Center 1) and the First Affiliated Hospital of Nanjing Medical University (Center 2) in China from August 2020 to August 2022. The exclusion criteria were as follows: (1) less than 18 years old; (2) had received HD for less than 3 months from initiation; (3) presence of fever, infection, or pregnancy; (4) fasting blood glucose over 11.1 mmol/L; (5) severe hepatic or pulmonary diseases, malignant tumors, or severe mental disorders; (6) episodes of acute myocardial infarction, stroke, or a major surgical procedure within the past 3 months. (7) refused the ECG and SKNA recordings. All the participants have provided written consent, and all the data were analyzed anonymously.

2.3. Data acquirement and processing

HD was performed under identical conditions. The dialysis machines used were Baxter Gambro AK96, AK98, and Fresenius 4008S models, with SSM160 and SSM180 high-flux dialyzers. Blood flow rates were standardized at 250 mL/min, and dialysis fluid was consistent across all patients.

Venous blood samples were collected in the morning before dialysis after overnight fasting. They were tested for hemoglobin, albumin, alkaline phosphatase, total cholesterol, triglyceride, serum potassium, serum calcium, serum phosphorus, intact parathyroid hormone (iPTH) and C-reactive protein (CRP). Systolic and diastolic blood pressures were measured at intervals of one hour from the initiation of HD and at any time when patients experienced discomfort symptoms.

SKNA and HRV were derived from single-lead high-frequency ECG, which was recorded continuously in all patients using homemade devices published previously [19]. Electrodes (3 M Red Dot Monitoring Electrode, #2570) were placed in the left subclavian, right subclavian, and right lower abdomen, respectively. Patients were required to stay supine in order to avoid moving during the signal recording process. Raw signals were bandpass filtered at 500–1000 Hz to calculate the average voltage of SKNA (aSKNA) as published before [20]. HRV parameters were derived using PhysioNet Cardiovascular Signal Toolbox by Vest et al. [21] including the mean value of sinus RR intervals (RRmean), standard deviation of normal-to-normal RR intervals (SDNN) the square root of the mean square of differences between adjacent normal-to-normal intervals (RMSSD), total power (TP), high-frequency power (HF), low-frequency power (LF), very low-frequency power (VLF), ultra low-frequency power (ULF), the ratio of low to high-frequency power (LF/HF), sample entropy (SampEn), and approximate entropy (ApEn).

We calculated 5-min HRV and aSKNA values at the start of dialysis (0 min) and at the 30 min of dialysis. Additionally, we calculated the rate of change. For example, the aSKNA value at the start of dialysis (0 min) is denoted as $aSKNA_0$, and the value at the 30th minute is denoted as $aSKNA_{30}$. The rate of change, referred to as $\triangle aSKNA_{0\text{-}30}$, is calculated as: $(aSKNA_{30}\text{-}aSKNA_0)/aSKNA_0$. Other parameters are calculated in the same manner.

2.4. Statistical analyses

The baseline characteristics were described using counts (percentages) for categorical variables. For continuous variables, we used mean ± standard deviation describing normally distributed variables and medians with interquartile ranges (IQRs) for non-normally distributed variables. Differences between groups were examined using chi-square tests for categorical variables and student t-tests or Mann–Whitney U test for continuous variables depending on the distribution of the dataset.

LASSO regression was used to select representative features of physiological parameters to predict IDH and minimize the effect of collinearity. We used the glmnet package in R software to establish the prediction model. The regularization parameter lambda, which was used to penalize the size of the coefficients of the model, was set as Lambda.min to construct the model.

Variables screened by LASSO regression were entered into a multivariate logistic regression model. Stepwise regression was performed using the minimum AIC criterion to build the final model. To evaluate the model, we generate the receiver operating characteristic (ROC) curve and assess the performance of the IDH prediction model by the area under the ROC curve (AUC) in the training cohort and the validation cohort, respectively. Calibration was assessed by comparing the observed IDH rates with predictions generated by the final model. Decision curve analysis (DCA) was conducted to evaluate the clinical benefits. A nomogram was developed based on the final multivariable logistic regression model.

All statistical analysis were performed using R software (version 4.2.1). A two-sided P value less than 0.05 was considered statistically significant.

3. Results

3.1. Study workflow

201 patients from two separate centers (103 from Center 1 and 98 from Center 2) were included. All patients received 4-hour HD and 90 of them developed IDH. These patients were divided randomly into a training set (70%, $n=136$) or a validation set (30%, $n=65$) for further analysis. Blood pressure was collected per hour and autonomic nervous activity was measured continuously. The flowchart and schematic diagram of this study are demonstrated in Figure 1.

3.2. Baseline characteristics

The demographic and baseline characteristics are detailed in Table 1. There was no significant difference between the two groups except those patients with IDH tended to be female (64/90 vs. 53/111, $p=0.018$), with higher serum triglyceride (1.98 (1.45, 2.81) vs. 1.58 (1.12, 2.40), $p=0.006$), and more usage of β-blocker (40/90 vs.33/111, $p=0.031$). IDH group showed higher systolic blood pressure (150.5 ± 22.3 vs. 140.4 ± 20.2 mmHg, $p=0.001$), while systolic blood pressure did not reach statistical significance (80.3 ± 12.5 vs. 77.0 ± 11.4 mmHg, $p=0.057$). In both IDH and non-IDH groups, systolic and diastolic blood pressure were lower at 2, 3, and 4 h of HD. Notably, in the IDH group, the blood pressure kept decreasing over four hours, whereas it remained relatively stable in the non-IDH group. The comparison of blood pressure changes is shown in Figure 2.

The representative HRV indices, including both time-domain and frequency-domain analyses, are presented in Table 2. There were no significant differences in the mean RR interval and LF/HF between the groups at baseline. However, the IDH group exhibited a lower baseline SDNN (33.6 (23.6, 40.1) vs. 21.4 (16.7, 28.2), $p<0.001$). The change of mean RR intervals (RRmean) from 0 to 30 min ($\triangle RRmean_{0\text{-}30}$) was significantly different between the IDH group and non-IDH group (0.01 (-0.01, 0.05) vs. 0.00 (-0.04, 0.02), $p=0.006$). Similarly, the change of SDNN ($\triangle SDNN_{0\text{-}30}$) also showed a significant difference (−0.16 (−0.35, −0.03) vs. 0.00 (−0.19, 0.17), $p<0.001$) between IDH and non-IDH patients. No difference was found in the change of LF/HF ($\triangle LF/HF_{0\text{-}30}$). As for SKNA, aSKNA were significantly higher in IDH patients than non-IDH patients at the start of HD (1.12 (0.89, 1.25) vs. 0.97 (0.83, 1.22), $p=0.014$). However, aSKNA at 30 min was lower in the IDH group than non-IDH group (0.92 (0.78, 1.23) vs. 1.14 (0.93, 1.35), $p<0.001$). The change of aSKNA during the first 30 min ($\triangle aSKNA_{0\text{-}30}$) was lower in IDH patients (-0.10 (-0.23, −0.04) vs. 0.14 (-0.01, 0.26), $p<0.001$).

3.3. Variable selection using LASSO regression and logistic regression

We randomly sampled 70% of the data as the training set ($n=136$) and 30% as the validation set ($n=65$). Model I was constructed using data from the initiation and 30 min of HD. 66 variables measured were included in the least absolute shrinkage and selection operator (LASSO) regression analysis. After LASSO regression selection (Figure 3), the following 8 variables remained significant predictors of IDH, including SBP_0, $aSKNA_0$, $\triangle aSKNA_{0\text{-}30}$, $SDNN_0$, $SampEn_0$, $\triangle RRmean_{0\text{-}30}$, $\triangle SDNN_{0\text{-}30}$, $\triangle LF/HF_{0\text{-}30}$. These 8 variables were included in the multivariate logistic regression model, and 5 variables were significant predictors of IDH (Table 3).

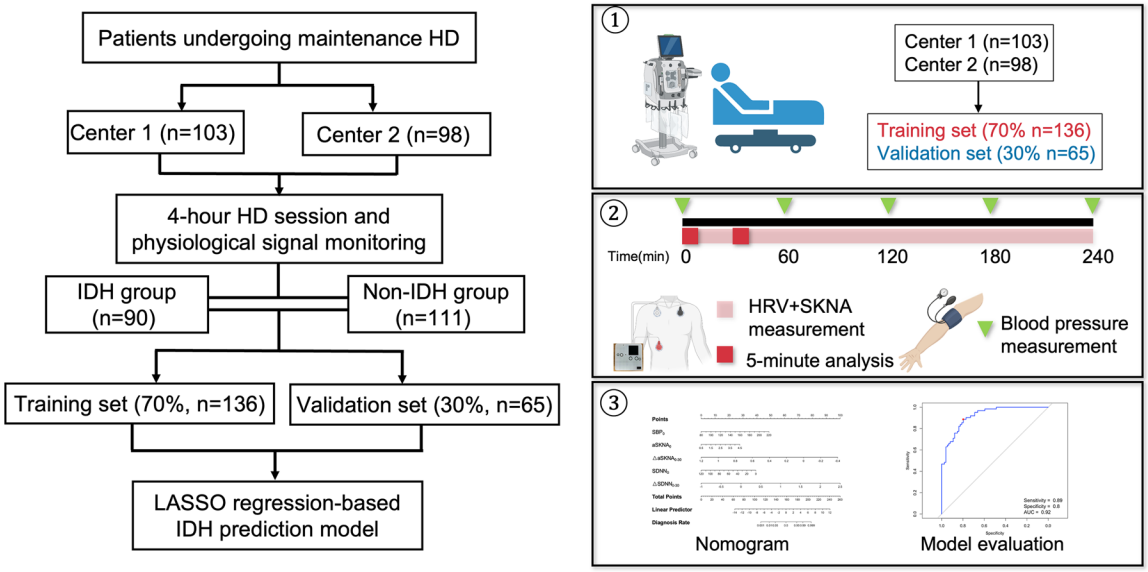

Figure 1. Study flowchart. The dataset used for model development consisted of HD patients from two distinct centers. The proposed model has the potential to identify high-risk IDH patients at an early stage of HD, facilitating proactive intervention and management strategies. Abbreviations: HD, hemodialysis; IDH, intradialytic hypotension; Centre 1, Nanjing Pukou People's Hospital; Centre 2, the First Affiliated Hospital of Nanjing Medical University; HRV, heart rate variability; SKNA, skin sympathetic nerve activity; BP, blood pressure.

Table 1. Comparison of the demographic and baseline characteristics in patients with or without IDH.

Variables	Total (n = 201)	Non-IDH (n =111)	IDH (n = 90)	p-value
Center, n (%)				0.146
1	103 (51.2)	62 (55.9)	41 (45.6)	
2	98 (48.8)	49 (44.1)	49 (54.4)	
SBP-0, mmHg	144.9 ± 21.7	140.4 ± 20.2	150.5 ± 22.3	0.001
DBP-0, mmHg	78.5 ± 12.0	77.0 ± 11.4	80.3 ± 12.5	0.057
MAP-0, mmHg	100.6 ± 12.8	98.1 ± 12.2	103.7 ± 13.0	0.002
SBP-1, mmHg	136.5 ± 19.9	136.5 ± 20.2	136.6 ± 19.5	0.975
DBP-1, mmHg	77.3 ± 11.1	77.5 ± 10.8	77.1 ± 11.5	0.820
MAP-1, mmHg	97.0 ± 12.2	97.1 ± 12.0	96.9 ± 12.5	0.904
SBP-2, mmHg	132.2 ± 22.9	136.5 ± 23.0	126.9 ± 21.7	0.003
DBP-2, mmHg	77.6 ± 12.5	78.9 ± 12.4	76.0 ± 12.6	0.105
MAP-2, mmHg	95.8 ± 14.3	98.1 ± 14.2	93.0 ± 14.1	0.012
SBP-3, mmHg	129.7 ± 24.3	137.2 ± 24.2	120.5 ± 21.1	< 0.001
DBP-3, mmHg	76.7 ± 12.8	79.2 ± 13.0	73.5 ± 11.8	0.001
MAP-3, mmHg	94.4 ± 14.9	98.6 ± 14.7	89.2 ± 13.4	< 0.001
SBP-4, mmHg	127.5 ± 23.6	136.3 ± 23.1	116.6 ± 19.3	< 0.001
DBP-4, mmHg	75.5 ± 12.2	78.1 ± 12.5	72.4 ± 11.2	< 0.001
MAP-4, mmHg	92.8 ± 14.5	97.5 ± 14.4	87.1 ± 12.5	< 0.001
Dry Weight, kg	62.4 (55.0, 70.1)	62.0 (53.4, 70.0)	62.8 (56.5, 70.2)	0.437
Volume, kg	2.47 ± 0.98	2.42 ± 0.97	2.54 ± 1.00	0.385
Volume/Dry weight (%)	3.85 ± 1.38	3.80 ± 1.41	3.90 ± 1.34	0.631
Age, years	60.0 (50.0, 70.0)	59.0 (49.5, 70.0)	63.5 (51.3, 71.0)	0.281
Sex, n (%)				0.018
Female	111 (55.2)	53 (47.7)	58 (64.4)	
Male	90 (44.8)	58 (52.3)	32 (35.6)	
Height, cm	168 (160, 172)	168 (162, 172)	165(158, 172)	0.223
BMI, kg/m^2	22.4 (20.6, 24.6)	22.1 (20.2, 24.4)	22.9 (20.8, 25.2)	0.069
Dialysis duration, months	9.0 (3.0, 60.0)	10.0 (4.0, 62.0)	6.0 (3.0, 55.3)	0.124
Hemoglobin, g/L	103.1 ± 17.0	102.2 ± 16.9	104.3 ± 17.2	0.368
Albumin, g/L	39.2 (36.8, 41.9)	39.4 (36.8, 42.3)	39.0 (36.9, 41.5)	0.574
ALP, IU/L	93.0 (71.5, 126.0)	89.0 (68.4, 118.9)	97.8 (76.2, 126.2)	0.157
TC, mmol/L	4.01 (3.40, 4.75)	4.00 (3.33, 4.49)	4.03 (3.41, 5.17)	0.309
TG, mmol/L	1.80 (1.22, 2.54)	1.58 (1.12, 2.40)	1.98 (1.45, 2.81)	0.006
Serum potassium, mmol/L	4.69 ± 0.68	4.72 ± 0.63	4.65 ± 0.74	0.524
Serum calcium, mmol/L	2.19 ± 0.23	2.18 ± 0.25	2.20 ± 0.22	0.492
Serum phosphorus, mmol/L	1.88 ± 0.51	1.86 ± 0.46	1.89 ± 0.57	0.684
CRP, mg/L	3.18 (1.41, 7.44)	3.04 (1.09, 6.86)	3.88 (1.68, 7.81)	0.134
iPTH, pg/mL	243 (108, 466)	223 (106, 397)	264 (123, 494)	0.325
DN, n (%)	62 (30.8)	34 (30.6)	28 (31.1)	0.942
PKD, n (%)	7 (3.5)	4 (3.6)	3 (3.3)	1.000
Hypertension, n (%)	161 (80.1)	86 (77.4)	75 (83.3)	0.392
β-blocker, n (%)	73 (36.3)	33 (29.7)	40 (44.4)	0.031
ACEI/ARB, n (%)	59 (27.9)	31 (28.0)	28 (31.1)	0.622
CCB, n (%)	89 (44.3)	48 (43.2)	41 (45.6)	0.743
Vitamin D, n (%)	82 (40.8)	49 (44.1)	33 (36.7)	0.283
Phosphate binder, n (%)	82 (40.8)	44 (39.6)	38 (42.2)	0.711

Abbreviations: IDH, intradialytic hypotension; Center 1, Nanjing Pukou People's Hospital; Center 2, the First Affiliated Hospital of Nanjing Medical University; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BMI, body mass index; ALP, alkaline phosphatase; TC, total cholesterol; TG, triglycerides; CRP, C-reactive protein; iPTH, intact parathyroid hormone; DN, diabetic nephropathy; PKD, polycystic kidney disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. *BP-0, 1, 2, 3, 4 represent the blood pressure measurements taken at the start of dialysis and at the 1st, 2nd, 3rd, and 4th hours of hemodialysis.

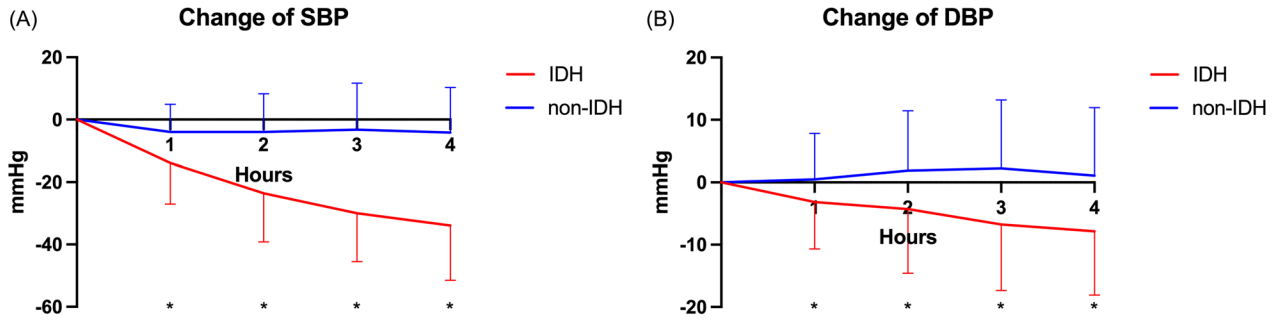

Figure 2. Changes in blood pressure in IDH and non-IDH patients. Abbreviations: IDH, intradialytic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure. '*' indicates statistical difference in change of SBP or DBP between IDH and non-IDH groups, $p < 0.05$.

Table 2. Comparison of representative HRV and SKNA parameters in patients with or without IDH.

Variables	Total (n = 201)	Non-IDH (n =111)	IDH (n = 90)	p-value
$RRmean_0$	800.7 (734.2, 906.1)	796.8 (728.9, 902.9)	817.2 (741.2, 913.3)	0.459
$RRmean_{30}$	827.0 ± 129.6	830.4 ± 139.3	822.7 ± 117.2	0.669
$\triangle RRmean_{0\text{-}30}$	0.01 (−0.02, 0.04)	0.01 (-0.01, 0.05)	0.00 (−0.04, 0.02)	0.006
$SDNN_0$	26.5 (20.1, 36.7)	33.6 (23.6, 40.1)	21.4 (16.7, 28.2)	<0.001
$SDNN_{30}$	22.5 (16.6, 33.0)	25.2 (17.1, 35.4)	20.2 (15.7, 30.6)	0.036
$\triangle SDNN_{0\text{-}30}$	−0.10 (−0.30, 0.09)	−0.16 (−0.35, −0.03)	0.00 (−0.19, 0.17)	<0.001
LF/HF_0	0.91 (0.48, 1.78)	1.03 (0.48, 1.74)	0.88 (0.46, 1.82)	0.756
LF/HF_{30}	1.06 (0.52, 2.21)	0.92 (0.52, 2.14)	1.16 (0.52, 2.27)	0.341
$\triangle LF/HF_{0\text{-}30}$	−0.06 (−0.34, 0.79)	−0.08 (−0.35, 0.76)	0.00 (−0.32, 1.12)	0.418
$aSKNA_0$	1.02 (0.86, 1.24)	0.97 (0.83, 1.22)	1.12 (0.89, 1.25)	0.014
$aSKNA_{30}$	1.04 (0.84, 1.32)	1.14 (0.93, 1.35)	0.92 (0.78, 1.23)	<0.001
$\triangle aSKNA_{0\text{-}30}$	−0.01 (−0.11, 0.17)	0.14 (−0.01, 0.26)	−0.10 (−0.23, −0.04)	<0.001

Abbreviations: IDH, intradialytic hypotension; aSKNA, the average voltage of skin sympathetic nerve activity; RRmean, the mean value of sinus RR intervals; SDNN, the standard deviation of normal-to-normal R-R intervals; RMSSD, root mean square of differences between adjacent normal R–R intervals; LF/HF, the ratio of low-frequency power to high-frequency power. *The subscript '0' indicates measurements taken at the start of dialysis, '30' represents measurements at 30 min into dialysis, and △0-30 denotes the change rate between 0 and 30 min."

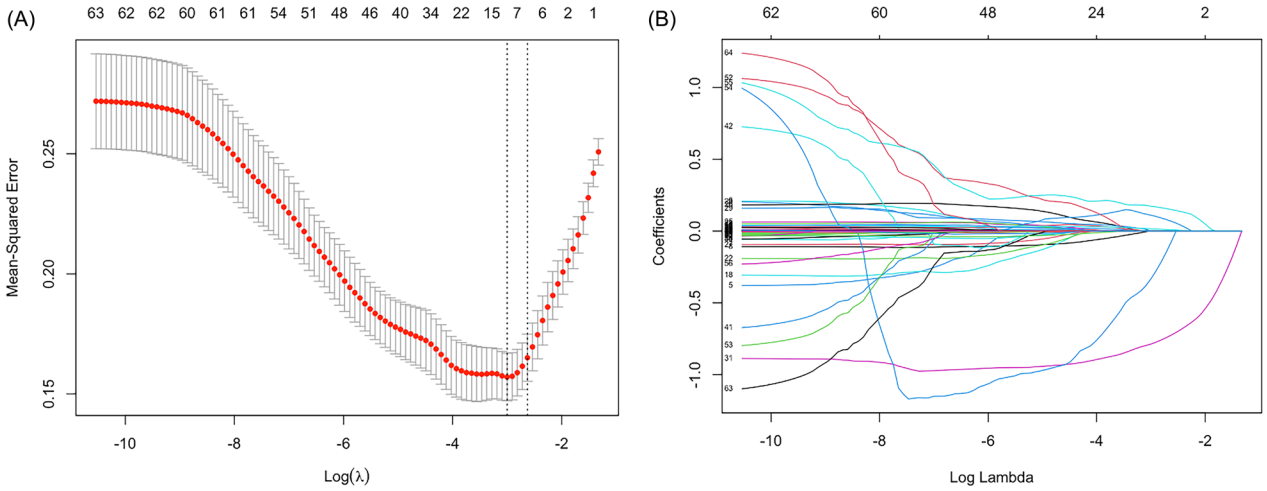

Figure 3. Using the LASSO binary logistic regression model to select variables. (A) Tuning parameter (λ) selection in the LASSO model used 10-fold cross-testing by minimum criteria. Eight variables were selected when log(λ) = -3.001. (B) LASSO coefficient profiles of the 66 features.

Table 3. LASSO-derived multivariate logistic regression model to predict IDH in the training cohort.

	Coefficients	Std.Error	Wald Z	p-value
SBP_0	0.051	0.018	2.960	0.003
$SDNN_0$	−0.046	0.019	−2.467	0.014
$SampEn_0$	1.524	0.800	1.905	0.057
$aSKNA_0$	1.059	0.505	2.098	0.036
$\triangle RRmean_{0\text{-}30}$	−8.555	4.684	−1.826	0.068
$\triangle SDNN_{0\text{-}30}$	3.233	1.220	2.651	0.008
$\triangle LF/HF_{0\text{-}30}$	0.306	0.189	1.620	0.106
$\triangle aSKNA_{0\text{-}30}$	−10.052	2.103	−4.781	<0.001

Abbreviations: IDH, intradialytic hypotension; Std.Error, standard error; SBP_0, systolic blood pressure at the beginning of dialysis; $SDNN_0$, standard deviation of normal-to-normal R-R intervals at the beginning of dialysis; $SampEn_0$, sample entropy at the beginning of dialysis; $aSKNA_0$, average voltage of skin sympathetic nerve activity at the beginning of dialysis; $\Delta RRmean_{0\text{-}30}$, change of mean value of sinus RR intervals during the first 30 min of dialysis; $\Delta SDNN_{0\text{-}30}$, change of standard deviation of normal-to-normal R-R intervals during the first 30 min of dialysis; $\Delta LF/HF_{0\text{-}30}$, change of the ratio of low-frequency power to high-frequency power during the first 30 min of dialysis; $\Delta aSKNA_{0\text{-}30}$, change of the ratio of average voltage of skin sympathetic nerve activity during the first 30 min of dialysis.

3.4. Construction of nomogram predicting IDH

Based on our multivariable logistic regression model, the nomogram was constructed using the following 5 variables: SBP_0, $aSKNA_0$, $\triangle aSKNA_{0\text{-}30}$, $SDNN_0$, $\triangle SDNN_{0\text{-}30}$ (Figure 4). Each variable was assigned a score based on its coefficient in the regression model. The cumulative score from these variables was used to predict the risk of IDH at the early stage of HD.

To demonstrate the application of the nomogram, consider a patient with the following initial values at the start of HD: SBP_0= 147 mmHg, $aSKNA_0$ = 0.89 μV, $\triangle aSKNA_{0\text{-}30}$ = −0.057, $SDNN_0$ = 12.45 ms, $\triangle SDNN_{0\text{-}30}$ = 0.02. Using the nomogram, each of these values is mapped to a corresponding score. The cumulative score is then calculated by adding up the scores from each variable. Based on the total score, the nomogram provides an estimated 78.6% probability of IDH for this patient, indicating a relatively high risk (Figure 4). This enables clinicians to make informed decisions on early interventions during the dialysis process.

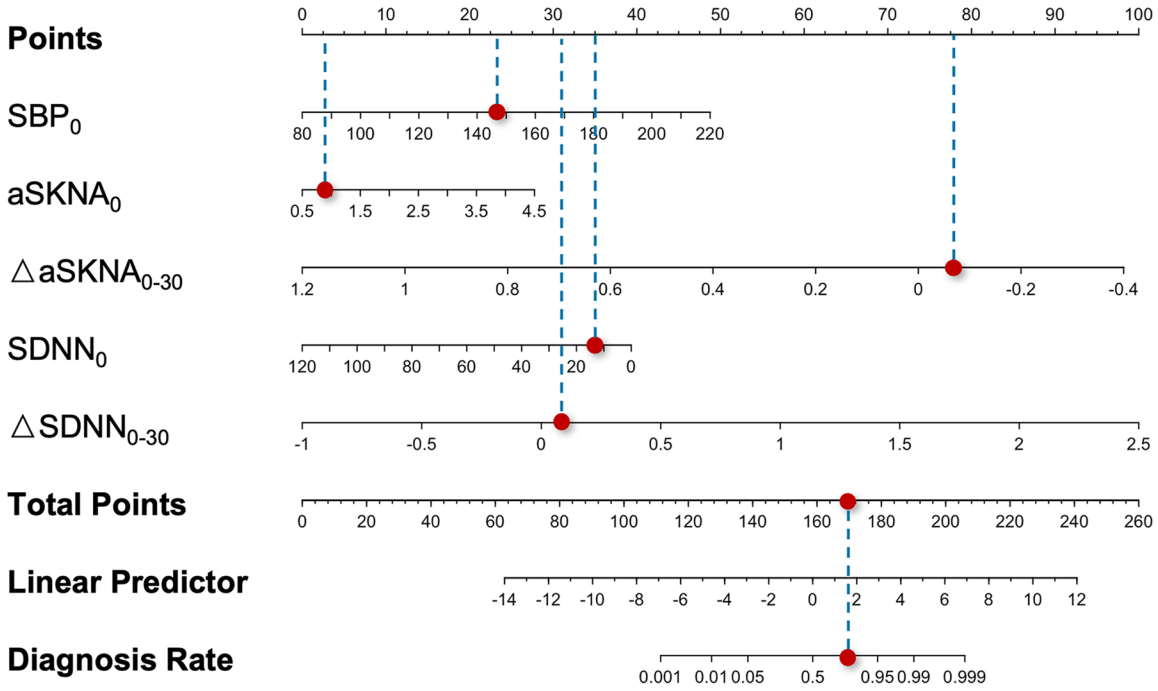

Figure 4. Nomogram and example use case for predicting the probability of IDH using data from the first 0-30 minutes of HD. The parameters of the case were shown in red dot. Abbreviations: IDH, intradialytic hypotension; SBP_0, systolic blood pressure at the beginning of dialysis; $aSKNA_0$, the average voltage of skin sympathetic nerve activity at the beginning of dialysis; $aSKNA_{0-30}$, the average voltage of skin sympathetic nerve activity during the first 30 minutes of dialysis; $SDNN_0$, the standard deviation of normal-to-normal R-R intervals at the beginning of dialysis; $\Delta SDNN_{0-30}$, change of standard deviation of normal-to-normal R-R intervals during the first 30 minutes of dialysis.

3.5. Model performance

In the training cohort, the area under the receiver operating characteristic (AUC) curve was 0.920 (95% CI, 0.878-0.962). We also performed independent validation of our nomogram in the validation cohort, which yielded an AUC value of 0.855 (95% CI, 0.763-0.947). The calibration curve revealed excellent concordance between the nomogram prediction and the actual observation of IDH. The decision curve analysis (DCA) shows that our final model provides benefits at various decision thresholds in both the training set and validation set, suggesting its strong clinical utility (Figure 5).

4. Discussion

The main findings of this study were as follows: First, we established the role of autonomic nervous regulation in the onset of IDH using noninvasive SKNA and HRV measurements. Second, we developed a useful model by LASSO-enabled feature selection to predict IDH early during HD, using data from two separate centers. Our work demonstrated the potential for early prediction of IDH using clinical information and physiological signals.

4.1. Autonomic dysfunction and IDH

Due to the discontinuous nature of HD, the accumulated fluid is quickly removed over several hours, placing a significant burden on the cardiovascular system, which makes blood pressure fluctuations common. Patients with IDH may exhibit symptoms such as dizziness, fatigue, nausea, and vomiting during dialysis, which can even lead to fainting and incomplete dialysis. IDH is associated with many risk factors, which can be mainly divided into patient-related factors such as age, higher body mass index, longer dialysis vintage, cardiac dysfunction and autonomous neuropathy, and HD-related factors including high ultrafiltration rate and conventionally used dialysate temperatures (such as 37–37.5 °C) [9]. The autonomic nervous system is highly sensitive to blood volume alteration and plays an important role in the maintenance of blood pressure. When autonomic function is impaired, patients may experience blood pressure instability during HD, including hypotension and hypertension [22], both of which are associated with higher mortality.

4.2. SKNA improved the prediction model for IDH

In previous studies, HRV has been applied to predict IDH. Chang et al. found that those who had SBP drop over 20 mmHg had significantly higher blood pressure at HD initiation and lower HRV indices, including variance, TP, VLF, LF, and HF since the middle phase of HD [10]. Their findings were mostly consistent with our observations. Compared with healthy individuals, HRV parameters in patients with chronic kidney disease are lower [23]. The reduced HRV indices represent cardiovascular ANS impairment and are independent predictors for the adverse outcome of chronic kidney disease [24]. In HD patients, those who had IDH showed even lower

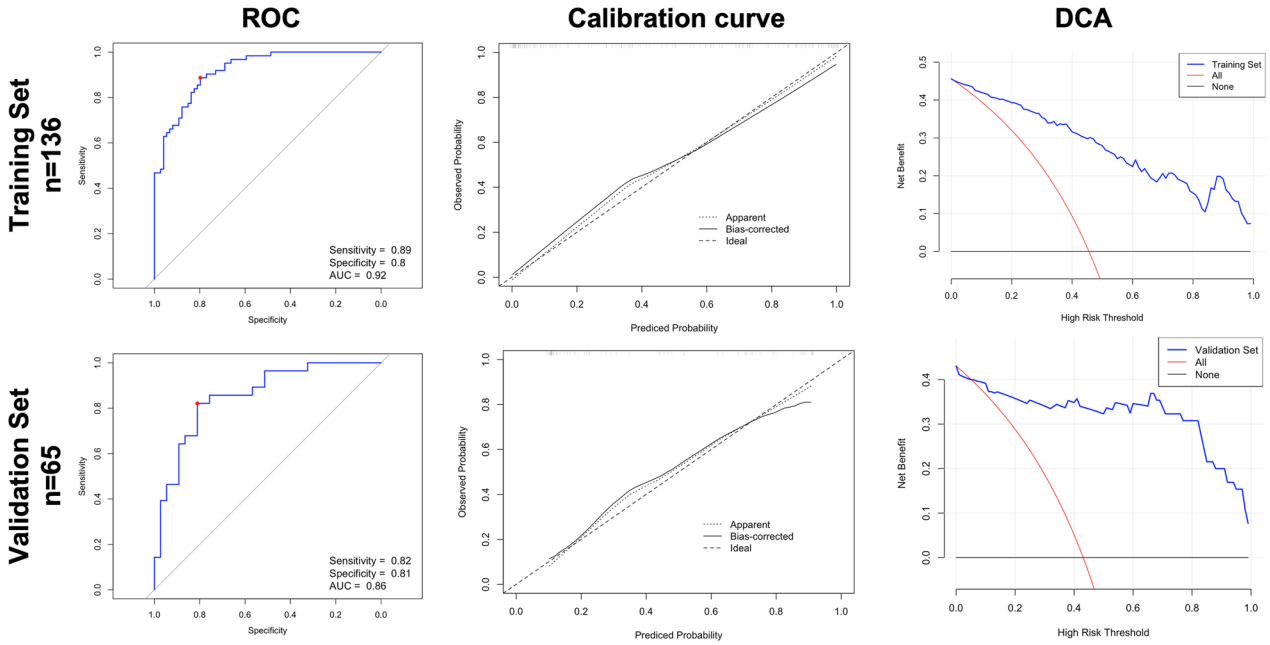

Figure 5. ROC curves, calibration curves, and decision curve analysis (DCA) of the nomogram for predicting IDH from the training set (n=136) and validation set (n=65). Abbreviations: IDH, intradialytic hypotension; AUC, the area under the ROC curve.

HRV indices. These data proved that HRV can help identify higher-risk patients in high-risk populations.

As a novel indicator of sympathetic nervous activity, SKNA signals were not included in previous models and are potential biomarkers for IDH prediction. SKNA can reflect the dynamic changes of the sympathetic state, which is sensitive to the slight changes of nerves. Our model further modifies the model by combining multiple signals and baseline information. Besides, to avoid individual differences in SKNA measurement, we used the rate of change of aSKNA over the first 30 min to indicate the relative alteration of sympathetic activity.

4.3. LASSO-regression-based model for IDH prediction

Different prediction models have been applied to the IDH prediction. Lee et al. [25] implied a deep learning-based artificial intelligence model using three recent HD sessions of clinical data and achieved the best predictive performance. Other AI or machine learning (ML) based models were also constructed to predict or early alert IDH before the start of HD [26,27]. Although these studies have established the ability of ML models in the prediction of IDH, the time-varying factors were not included. Real-time IDH models were developed to predict IDH, which are more useful in clinical practice for early decision-making during HD [28,29]. Dynamic parameters, like body temperature, blood pressure, and heart rate, were included, while the indices reflecting ANS function were not. In our findings, the changes of HRV and SKNA at the first 30 min of HD can predict IDH. These findings suggest the prospect of real-time prediction of IDH using the ANS parameters. Given the large number of parameters and the potential for multicollinearity, we employed LASSO regression to select the most relevant variables and optimized the regression model. To enhance the generalizability of the model, we included patients from two separate HD centers. Our model achieved an AUC of 0.85 at the validation cohort and exhibited good discriminative ability. It implies that this model may assist clinicians proactively and real-timely intervening in patients at risk for IDH.

The high prevalence and poor prognosis of IDH emphasize the need for early detection in the process of HD and optimizing preventive strategies. However, we can only deal with IDH when the blood pressure decreases or the patients present with hypotension-related symptoms. Early parameters or biomarkers can help clinicians identify those high-risk patients. Hopefully, with this model, we can screen for higher-risk patients in the early stages of HD. When determining these high-risk populations, we can initiate interventions such as adjusting the composition and temperature of the dialysis solution, controlling the ultrafiltration rate appropriately, and adjusting medication therapy.

5. Conclusion

Our LASSO-enabled logistic regression model, which incorporates clinical information and autonomic nervous parameters (HRV and SKNA) at the initiation of HD, can predict the occurrence of IDH, offering a potential for early alerts and improved clinical outcomes for HD patients at risk.

6. Limitations

There are some limitations in this study. Firstly, a total of 201 patients were enrolled in our research, but the sample size is relatively small, which may limit the generalizability of our

findings. Secondly, this study did not monitor the dynamic changes in blood pressure in real-time, so we could not fully explore the data to further elucidate the characteristics of autonomic nervous system changes before and after blood pressure changes.

Ethics statement

The research has been carried out in accordance with the World Medical Association Declaration of Helsinki, and all subjects provided written informed consent.

Authors' contributions

All authors contributed to the conception and design of the study. Acquisition of data was done by S. Su, Z. Chen, Y. Huang, and Y. Qian. Y. Xing was responsible for the equipment maintenance and algorithm support. Y. Zhang performed the statistical analyses and wrote the first draft of the manuscript. C. Chang, H. Chen, N. Wang, H. Mao, and J. Wang reviewed and polished the manuscript. All authors revised the manuscript thoroughly and have approved the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by grants from the National Natural Science Foundation of China (No.81970639 and No.82170322), and the Scientific Research Project of Jiangsu Provincial Health and Wellness Commission (No.H2017023).

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

References

[1] Kuipers J, Verboom LM, Ipema KJR, et al. The prevalence of intradialytic hypotension in patients on conventional hemodialysis: a systematic review with meta-analysis. Am J Nephrol. 2019;49(6):497–506. doi: 10.1159/000500877.

[2] Saran R, Robinson B, Abbott KC, et al. US renal data system 2018 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2019;73(3 Suppl 1):A7–A8. doi: 10.1053/j.ajkd.2019.01.001.

[3] Chou JA, Streja E, Nguyen DV, et al. Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. Nephrol Dial Transplant. 2018;33(1):149–159. doi: 10.1093/ndt/gfx037.

[4] Sars B, van der Sande FM, Kooman JP. Intradialytic hypotension: mechanisms and outcome. Blood Purif. 2020;49(1–2):158–167. doi: 10.1159/000503776.

[5] Stefánsson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. Clin J Am Soc Nephrol. 2014;9(12):2124–2132. doi: 10.2215/CJN.02680314.

[6] Kanbay M, Ertuglu LA, Afsar B, et al. An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. Clin Kidney J. 2020;13(6):981–993. doi: 10.1093/ckj/sfaa078.

[7] Yu J, Liu Z, Shen B, et al. Intradialytic hypotension as an independent risk factor for long-term mortality in maintaining hemodialysis patients: a 5-year follow-up cohort study. Blood Purif. 2018;45(4):320–326. doi: 10.1159/000486231.

[8] Wu Y, Lu J, Wang T, et al. Association of frequent intradialytic hypotension with the clinical outcomes of patients on hemodialysis: a prospective cohort study. Ren Fail. 2024;46(1):2296612. doi: 10.1080/0886022X.2023.2296612.

[9] van der Sande FM, Dekker MJ, Leunissen KML, et al. Novel insights into the pathogenesis and prevention of intradialytic hypotension. Blood Purif. 2018;45(1–3):230–235. doi: 10.1159/000485160.

[10] Chang YM, Shiao CC, Chang KC, et al. Heart rate variability is an indicator for intradialytic hypotension among chronic hemodialysis patients. Clin Exp Nephrol. 2016;20(4):650–659. doi: 10.1007/s10157-015-1189-9.

[11] Park S, Kim WJ, Cho NJ, et al. Predicting intradialytic hypotension using heart rate variability. Sci Rep. 2019;9(1):2574. doi: 10.1038/s41598-019-39295-y.

[12] Doytchinova A, Hassel JL, Yuan Y, et al. Simultaneous noninvasive recording of skin sympathetic nerve activity and electrocardiogram. Heart Rhythm. 2017;14(1):25–33. doi: 10.1016/j.hrthm.2016.09.019.

[13] Kusayama T, Wong J, Liu X, et al. Simultaneous noninvasive recording of electrocardiogram and skin sympathetic nerve activity (neuECG). Nat Protoc. 2020;15(5):1853–1877. doi: 10.1038/s41596-020-0316-6.

[14] He W, Tang Y, Meng G, et al. Skin sympathetic nerve activity in patients with obstructive sleep apnea. Heart Rhythm. 2020;17(11):1936–1943. doi: 10.1016/j.hrthm.2020.06.018.

[15] Meng G, He W, Wong J, et al. Successful continuous positive airway pressure treatment reduces skin sympathetic nerve activity in patients with obstructive sleep apnea. Heart Rhythm. 2022;19(1):127–136. doi: 10.1016/j.hrthm.2021.09.018.

[16] Wang W, Cheng H, Zhang Y, et al. Skin sympathetic nerve activity as a biomarker for outcomes in spontaneous intracerebral hemorrhage. Ann Clin Transl Neurol. 2023;10(7):1136–1145. doi: 10.1002/acn3.51795.

[17] Xing Y, Cheng H, Yang C, et al. Evaluation of skin sympathetic nervous activity for classification of intracerebral hemorrhage and outcome prediction. Comput Biol Med. 2023;166:107397. doi: 10.1016/j.compbiomed.2023.107397.

[18] Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. Nephrol Dial Transplant. 2007;22 Suppl 2(Supplement 2):ii22–44. doi: 10.1093/ndt/gfm019.

[19] Xing Y, Zhang Y, Yang C, et al. Design and evaluation of an autonomic nerve monitoring system based on skin

sympathetic nerve activity. Biomed Signal Process Control. 2022;76:103681. doi: 10.1016/j.bspc.2022.103681.
[20] Zhang Y, Wang J, Xing Y, et al. Dynamics of cardiac autonomic responses during hemodialysis measured by heart rate variability and skin sympathetic nerve activity: the impact of interdialytic weight gain. Front Physiol. 2022;13:890536. doi: 10.3389/fphys.2022.890536.
[21] Vest AN, Da Poian G, Li Q, et al. An open source benchmarked toolbox for cardiovascular waveform and interval analysis. Physiol Meas. 2018;39(10):105004. doi: 10.1088/1361-6579/aae021.
[22] Assimon MM, Flythe JE. Intradialytic blood pressure abnormalities: the highs, the lows and all that lies between. Am J Nephrol. 2015;42(5):337–350. doi: 10.1159/000441982.
[23] Zhang LN, Yang G, Cheng C, et al. Plasma FGF23 levels and heart rate variability in patients with stage 5 CKD. Osteoporos Int. 2015;26(1):395–405. doi: 10.1007/s00198-014-2862-7.
[24] Gao X, Wang J, Huang H, et al. Nomogram model based on clinical risk factors and heart rate variability for predicting all-cause mortality in stage 5 CKD patients. Front Genet. 2022;13:872920. doi: 10.3389/fgene.2022.872920.
[25] Lee H, Moon SJ, Kim SW, et al. Prediction of intradialytic hypotension using pre-dialysis features-a deep learning-based artificial intelligence model. Nephrol Dial Transplant. 2023;38(10):2310–2320. doi: 10.1093/ndt/gfad064.
[26] Hong D, Chang H, He X, et al. Construction of an early alert system for intradialytic hypotension before initiating hemodialysis based on machine learning. Kidney Dis (Basel). 2023;9(5):433–442. doi: 10.1159/000531619.
[27] Yang X, Zhao D, Yu F, et al. Boosted machine learning model for predicting intradialytic hypotension using serum biomarkers of nutrition. Comput Biol Med. 2022;147:105752. doi: 10.1016/j.compbiomed.2022.105752.
[28] Zhang H, Wang LC, Chaudhuri S, et al. Real-time prediction of intradialytic hypotension using machine learning and cloud computing infrastructure. Nephrol Dial Transplant. 2023;38(7):1761–1769. doi: 10.1093/ndt/gfad070.
[29] Lee H, Yun D, Yoo J, et al. Deep learning model for real-time prediction of intradialytic hypotension. Clin J Am Soc Nephrol. 2021;16(3):396–406. doi: 10.2215/CJN.09280620.