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Construction of an Early Alert System for Intradialytic Hypotension before Initiating Hemodialysis Based on Machine Learning

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Keywords
Intradialytic hypotension · Hemodialysis · Alert system · Artificial intelligence · Machine learning

Abstract
Introduction: Intradialytic hypotension (IDH) is prevalent and associated with high hospitalization and mortality rates. The purpose of this study was to explore the risk factors for IDH and use artificial intelligence to establish an early alert system before hemodialysis sessions to identify patients at high risk of IDH. ***Materials and Methods:*** We obtained data on 314,534 hemodialysis sessions conducted at Sichuan Provincial People's Hospital from the renal disease treatment information system. IDH was defined as a systolic blood pressure drop ≥20 mm Hg, a mean arterial pressure drop ≥10 mm Hg during dialysis, or the occurrence of clinical hypotensive events requiring nursing intervention. After pre-processing, the data were randomly divided into training (80%) and testing (20%) sets. Four interpolation methods, three feature selection methods, and 18 machine learning algorithms were used to construct predictive models. The area under the receiver operating characteristic curve (AUC) was the main indicator for evaluating the performance of the models, while Shapley Additive ExPlanation was used to explain the contribution of each variable to the best predictive model. ***Results:*** A total of 3,906 patients and 314,534 dialysis sessions were included, of which 142,237 cases showed IDH (incidence rate, 45.2%). Nineteen parameters were identified through artificial intelligence feature screening. They included age, pre-dialysis weight, dry weight, pre-dialysis blood pressure, heart rate, prescribed ultrafiltration, blood cell counts (neutrophil, lymphocyte, monocyte, eosinophil, lymphocyte, and platelet counts), hematocrit, serum calcium, creatinine, urea, glucose, and uric acid. Random forest, gradient boosting, and logistic regression were the three best models, and the AUCs were 0.812 (95% confidence interval [CI], 0.811–0.813), 0.748 (95% CI, 0.747–0.749), and 0.743 (95% CI, 0.742–0.744), respectively. ***Conclusion:*** Our dialysis software-based artificial intelligence alert system can be used to predict IDH occurrence, enabling the initiation of relevant interventions.

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Introduction

Intradialytic hypotension (IDH) is one of the most common complications during hemodialysis [1, 2] and is an important risk factor for cardiovascular events, hospitalization, and mortality [3–5]. The reported incidence of IDH ranges from 7.5% to 69% according to different definitions [6, 7]. According to the recommended definition from the Kidney Disease Outcome Quality Initiative (KDOQI), the incidence rate is 20–30% [4]. The mechanism of IDH is complicated and associated with decreased blood volume and insufficient vascular response [8, 9]. The occurrence of IDH depends on various risk factors, including demographic factors (age, sex), comorbidities (diabetes, coronary heart disease, left ventricular hypertrophy), dialysis characteristics, complications (dialysis vintage, weight gain between dialysis sessions, anemia), dialysis treatment prescription (ultrafiltration), medications (antihypertensive medications), and laboratory findings [10–12]. Therefore, pre-assessment and monitoring of all patients during hemodialysis are critical for IDH prevention and treatment [13]. However, IDH is associated with many factors and is difficult to predict, even for experienced nephrologists. Many efforts have been made to predict and initiate interventions to prevent IDH. However, in clinical settings, accuracy and applicability remain poor.

Artificial intelligence (AI) is a branch of computer science that can analyze complex medical data and can be used for clinical diagnosis, treatment, prediction, and efficacy evaluation [14]. Machine learning can merge a large amount of different data into a unified algorithm, such that a large amount of data can be used to develop reliable predictive analysis [15]. AI has been applied to predict IDH [13, 16–19]; however, they can only predict IDH more than 1 h after initiating hemodialysis, which compromises the possibility of early intervention. The purpose of this study was to establish a software-based early alert system using AI to identify patients at high risk of IDH just before the initiation of hemodialysis, thereby allowing the medical team to manage and prevent IDH during hemodialysis.

Materials and Methods

Data Sources

Data of all patients who underwent hemodialysis between 2014 and 2020 were obtained from the renal disease treatment information system in Sichuan Provincial People's Hospital. All data were de-identified. Variables were extracted from renal disease treatment information system. The variables are shown in Table 1.

Definition of IDH

IDH, which was set as the target output, was defined as a systolic blood pressure (SBP) drop ≥20 mm Hg, a mean arterial pressure drop ≥10 mm Hg during dialysis, or the occurrence of clinical hypotensive events requiring nursing intervention [20].

Model Development

Data Pre-Processing

Data Pre-Screening. After de-identification, all data had to pass a three-step screening process: (1) deletion of columns with a ratio of missing data more than 90%; (2) deletion of columns with a single category ratio of more than 90%; and (3) deletion of columns with a coefficient of variation less than 0.1.

Data Filling. As missing data were inevitable, four different methods were used to fill in the data: no imputation, simple imputation, random forest imputation, and improved random forest imputation [21–23].

Feature Screening. Three methods were applied in feature screening: no screening, Lasso screening [24, 25], and Boruta screening [26]. The feature selection algorithm outputs feature importance for each variable. The higher the feature importance value, the greater the influence of this variable on the result. After exportation, the data were desensitized, and the analyst did not know the meaning of each parameter, which to a certain extent avoided errors caused by the analyst's subjective belief that the parameter was meaningless.

Model Construction. Four filling methods and three feature screening methods were used to obtain 12 datasets. Eighteen machine learning algorithms, including logistic regression [27, 28], Latent Dirichlet allocation [29], Quadratic Discriminant Analysis [30], Stochastic Gradient Descent [31], k-Nearest Neighbor [32], Decision Tree [33], Naive Bayes [34], Gaussian Naïve Bayes [35], Multinomial Naive Bayes [36], Bernoulli Naïve Bayes [37], Support Vector Machine [38], passive-aggressive [39], AdaBoost [40], bagging, Random Forest [41], Extremely Randomized Trees [42], gradient boosting [41], XGBoost [43], and ensemble learning [44], were used to train 216 models. The process of building the models was as follows:

(1) The dataset was randomly divided into a training and a test set in a ratio of 8:2.
(2) The training set data were entered into the machine learning model, and the 10-fold cross-validation method was used to continuously adjust the model parameters, so that the parameters had the largest area under the receiver operating characteristic curve (AUC) value on the training set. According to the voting principle, the ensemble algorithm outputs the results of the five models with the best training performance for each dataset, as judged by the AUC value.

The test set was sampled 200 times using the bootstrap method. These re-sampled new datasets were entered into the model for external verification of all models. The test set data were entered into the trained model for model verification. Based on the AUC values, the best model was obtained.

Model Evaluation. AUC, accuracy, precision, recall, and the F1 score (the F1 value is the harmonic mean of precision and recall [45]. If only the precision or recall rate is considered, it cannot be

Table 1. Variables extracted from RTS

Classification	Variables
Demographic data	Sex, age, body weight
Clinical data	
Primary disease	Chronic glomerulonephritis, diabetic nephropathy
Comorbidities	Hypertension, diabetes, cardiovascular disease
Complications	Renal anemia, renal bone disease
Dialysis-related records	Dialysis vintage, weekly hemodialysis frequency, dialysis session time, post-dialysis body weight, interdialytic weight gain, dry weight, prescribed ultrafiltration, pre-dialysis blood pressure, mean arterial pressure, dialysate temperature, dialysate sodium, and dialysate calcium

used as an indicator to evaluate a model. Therefore, the F1 value was used to reconcile the two, which is compatible with precision and recall rates) were used to evaluate model performance. The best performing model was selected as the predictive model. The Shapley Additive ExPlanation was used to explain the contribution of each variable to the best predictive model. The modeling process is shown in Figure 1.

Sample Size Verification

The best model was used for sample size verification. We randomly sampled 10%, 20%, 30%, and 100% of the data from the training set by replacing the resampling method to train the model to generate 10 different AUC values on the test set. This process was repeated 100 times to obtain the AUC, and a line graph was drawn based on this value; the change in the inflection point of the line graph was used to determine whether the performance of the model could be improved by increasing the sample size. Qualitative data are presented as frequencies, and quantitative data are presented as means ± standard deviations. Analysis of variance and rank sum tests were used for the univariate analysis. Statistical analysis was implemented using stats in Python 3.8, and prediction models were built using sklearn in Python 3.8.

Results

In the test set, the IDH incidence rate was 45.2%. The average age of the patients was 60.7 ± 14.3 years, 58% were men, and more than 90% were conventional hemodialysis patients. Dialysis access, in more than 90% of patients was through an arteriovenous fistula. Other baseline characteristics are shown in Table 2. Using the test dataset, the best performing model was the random forest with an AUC of 0.812 (95% confidence interval [CI], 0.811–0.813); accuracy of 0.740 (95% CI: 0.739–0.741); precision of 0.732 (95% CI, 0.731–0.734); recall of 0.669 (95% CI, 0.667–0.670); and F1 of 0.699 (95% CI, 0.698–0.700). The second-best model was gradient boosting, with an AUC of 0.748 (95% CI, 0.747–0.749).

The AUC and precision-recall curve for predicting IDH were higher for the random forest model than those for the other machine learning models and logistic regression models (Fig. 2). Table 3 summarizes the 13 models. As illustrated by Figure 2, the same dataset, the ROC, and PR curves intersected, which means that it is difficult to identify the better model using PR curve or the ROC curve; therefore, we further calculated the F1 value. Table 4 summarizes the five best performing models, where the F1 score of random forest is higher than that of the other models.

Feature Importance Ranking Analysis

To estimate the contribution of each feature in predicting the risk of IDH, we used three feature screening methods for feature ranking analysis. When building the model, each feature was deleted from the test dataset and the prediction results were compared with the reference prediction results of all the features (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000531619).

Sensitivity Analysis

The patients were randomly divided into a training set (80%) and a test set (20%) to build a model. This was performed to balance the characteristics of the patients and the number of hemodialysis sessions for each patient. Using this randomization method, the model predicted the manner in which IDH was similar to before.

Discussion

IDH is a common occurrence in patients on hemodialysis. According to the KDOQI guidelines, approximately 20–30% of patients have IDH [4] and it occurs at least once in 75% of patients on hemodialysis [46]. In

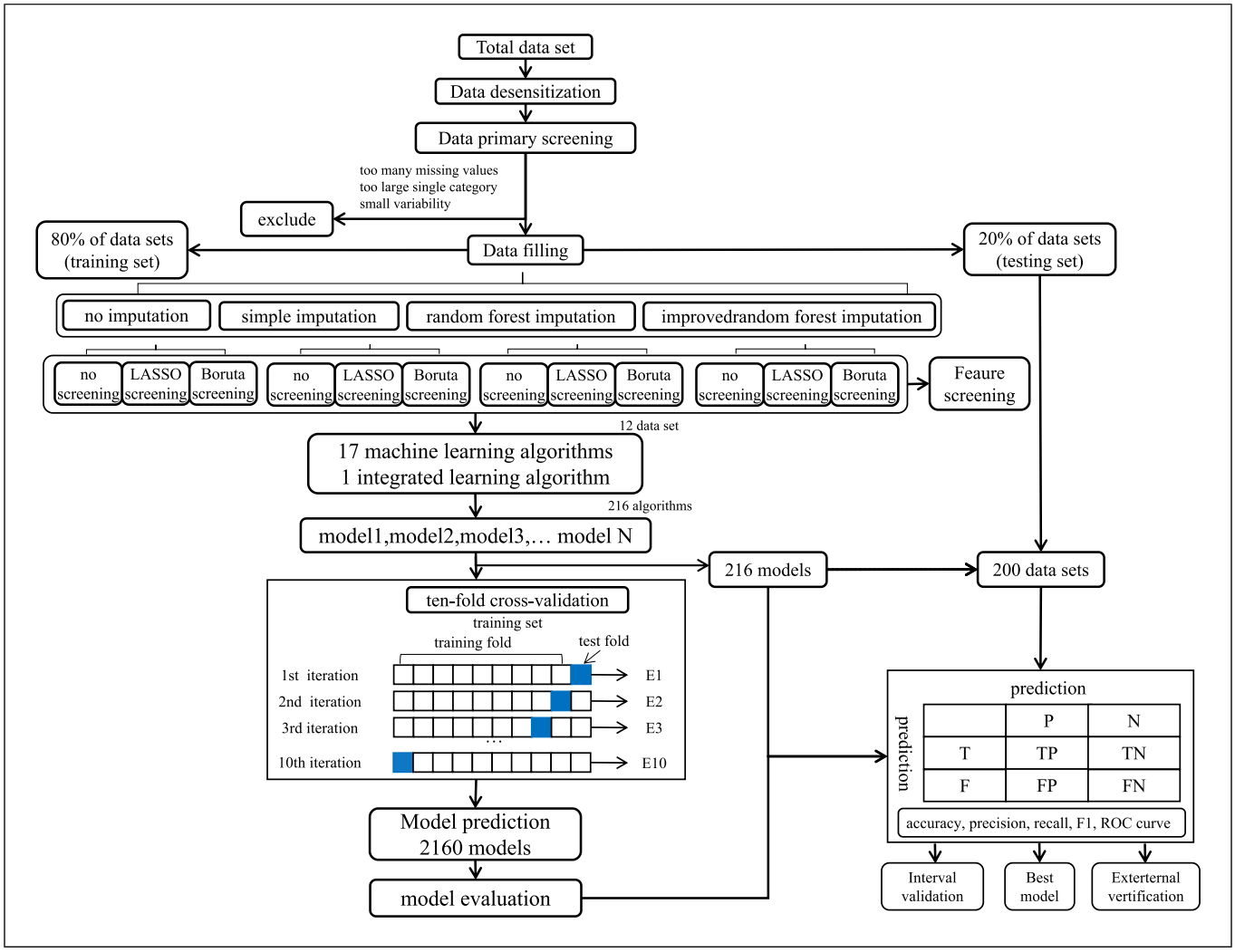

Fig. 1. Flow chart of machine learning model construction. TP, true positive; FN, false negative; FP, false positive; TN, true negative. Accuracy = (TP + TN)/(TP + FN + FP + TN), precision = TP/(TP + FP), recall = TP/(TP + FN), F1 = 2 * (precision* recall)/(precision+ recall).

our study, we found that IDH occurred in 45.2% of dialysis sessions, which appears to be higher than that in other centers, given that single-center studies are limiting, we plan to verify it further through a multi-center study.

IDH is associated with many adverse events, and there is a direct linear relationship between IDH frequency and mortality [17].Other adverse events include cardiovascular events [47], hospitalization, arteriovenous thrombosis [48], loss of residual renal function [49], cerebral ischemia [11], and mesenteric ischemia [50, 51]. Although hemodialysis technology continues to evolve, the incidence of hypotension during dialysis has not decreased significantly, possibly because of the many complex variables involved. Therefore, IDH is difficult to predict. Although AI has been used to predict the occurrence of IDH [13, 16–19, 52], the definitions of IDH are variable, resulting in IDH prediction rates of 9.7–51% and AUCs of 0.793–0.904. Previous models collected all parameter data during hemodialysis and could only predict IDH 1 h after hemodialysis initiation. However, the first hour of dialysis is the peak period of IDH occurrence [53]. Therefore, we used variables that could be obtained just before the initiation of hemodialysis treatment, which will allow the medical team to adjust prescriptions or initiate relevant management to prevent the occurrence of IDH.

Table 2. Baseline characteristics of the hemodialysis sessions

Variables	Total
Age, years	60.7±14.3
Male, *n*, (%)	2,266 (58.01)
The number of sessions per week, times	3
The time per session, h	3.9±0.3
Pre-dialysis weight, kg	60.6±11.5
Setting of ultrafiltration, L	2.0±1.3
Pre-dialysis systolic BP, mm Hg	138.8±22.7
Pre-dialysis diastolic BP, mm Hg	71.2±16.4
Pre-dialysis mean arterial pressure, mm Hg	93.7±18.5
Pre-dialysis heart rate, beats/min	77.3±13.3
Blood findings	
Hemoglobin, g/L	109.8±17.5
Albumin, g/L	39.9±3.55
Calcium, mmol/L	2.3±0.28
Phosphate, mmol/L	1.8±0.57
Sodium, mmol/L	137.9±4.12
Potassium, mmol/L	4.8±0.79
PTH, pg/mL	487.6±420.51
FER, pg/mL	381.6±301.02
Dialysate prescription	
Dialysate sodium, mmol/L	138
Dialysate potassium, mmol/L	3
Dialysate calcium, mmol/L	1.25
Dialysate bicarbonate, mmol/L	31
Dialysate temperature, °C	36 (35–37)

[a]Total number of patients was 3,906.

We used machine learning to screen risk factors and attempted to find intervention points. We eventually included a total of 19 parameters, including demographic characteristics, laboratory tests, and dialysis-related records.

In terms of clinical credibility, the most important variables found in our study were consistent with those of previous studies such as age, pre-dialysis body weight, dry body weight, pre-dialysis blood pressure, heart rate, and prescribed ultrafiltration. Previous studies had shown that age, pre-dialysis weight, dry weight, pre-dialysis blood pressure, heart rate, prescribed ultrafiltration, and hematocrit can be used as prediction indicators of intradialytic hypotension. Some studies have used these parameters to predict the occurrence of IDH. Older age may cause autonomic dysfunction, reduce baroreceptor sensitivity, and induce hypotension during dialysis. Concurrently, older patients are often complicated with hypertension, diabetes, heart disease, and other basic diseases, and IDH is more likely to occur. The relationship between the body mass index and IDH has been inconsistently reported [54]. Some studies reported that high body weight before dialysis can lead to hemodynamic instability, which may be related to the increase in abdominal pressure caused by obesity and the increase in venous reflux resistance [55]. The correlation between dry weight and ultrafiltration and IDH is clear. If the dry

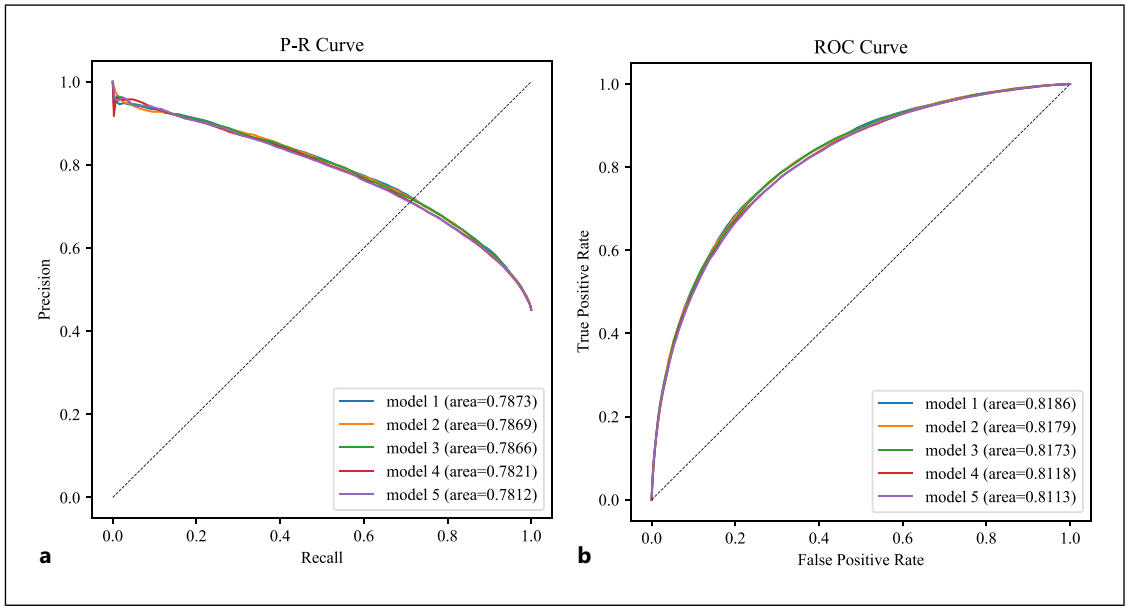

Fig. 2. Precision-recall (**a**) and receiver-operating characteristic (**b**) curves for the prediction of intradialytic hypotension (IDH). RF, random forest; GB, gradient boosting; LR, logistic regression; SGD, Stochastic Gradient Descent; LDA, Latent Dirichiet allocation.

Table 3. Area under the curves for predicting intradialytic hypotension for the four models used in this study

Outcome	Models	AUC		Accuracy		Precision		Recall		F1 score	
		mean ± SD	95% CI	mean ± SD	95% CI	mean ± SD	95% CI	mean ± SD	95% CI	mean ± SD	95% CI
IDH	Random_Forest	0.812±0.006	0.811–0.813	0.740±0.006	0.739–0.741	0.732±0.007	0.731–0.734	0.669±0.008	0.667–0.670	0.699±0.007	0.698–0.700
	Gradient_Boosting	0.748±0.006	0.747–0.749	0.685±0.005	0.684–0.686	0.687±0.008	0.686–0.689	0.556±0.006	0.554–0.557	0.614±0.006	0.613–0.616
	Logistic_Regression	0.743±0.007	0.742–0.744	0.682±0.006	0.681–0.683	0.665±0.007	0.664–0.666	0.596±0.008	0.595–0.598	0.629±0.007	0.627–0.630
	SGD	0.743±0.007	0.741–0.744	0.682±0.006	0.680–0.683	0.669±0.007	0.667–0.670	0.586±0.010	0.584–0.587	0.624±0.008	0.623–0.626
	LDA	0.741±0.007	0.740–0.742	0.680±0.006	0.679–0.681	0.666±0.007	0.665–0.667	0.586±0.009	0.584–0.588	0.623±0.007	0.622–0.625
	AdaBoost	0.734±0.006	0.733–0.735	0.674±0.005	0.673–0.675	0.667±0.006	0.666–0.669	0.555±0.010	0.553–0.557	0.606±0.007	0.605–0.607
	QDA	0.730±0.010	0.728–0.732	0.673±0.007	0.672–0.675	0.666±0.021	0.663–0.670	0.560±0.035	0.554–0.566	0.607±0.014	0.605–0.610
	Decision_Tree	0.720±0.005	0.719–0.721	0.666±0.004	0.666–0.667	0.668±0.014	0.666–0.671	0.523±0.037	0.516–0.530	0.586±0.018	0.582–0.589
	Extra_Tree	0.716±0.013	0.714–0.718	0.666±0.010	0.664–0.668	0.659±0.014	0.656–0.661	0.543±0.028	0.538–0.548	0.595±0.018	0.591–0.598
	Gaussian_Naive_Bayes	0.692±0.018	0.689–0.695	0.643±0.026	0.639–0.648	0.625±0.043	0.617–0.633	0.566±0.092	0.550–0.583	0.587±0.024	0.583–0.591
	Bernoulli_Naive_Bayes	0.686±0.009	0.685–0.688	0.644±0.008	0.642–0.645	0.611±0.008	0.610–0.613	0.581±0.011	0.579–0.583	0.596±0.009	0.594–0.598
	Passive_Aggressive	0.613±0.042	0.605–0.620	0.582±0.033	0.576–0.588	0.539±0.039	0.532–0.546	0.557±0.063	0.546–0.569	0.545±0.036	0.539–0.552
	Multinomial_Naive_Bayes	0.558±0.005	0.557–0.559	0.555±0.005	0.554–0.556	0.370±0.263	0.323–0.418	0.082±0.065	0.070–0.093	0.132±0.101	0.113–0.150
	p value	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	

weight value is too low, the ultrafiltration rate will be too fast and too high, resulting in the ultrafiltration volume being far higher than the tissue fluid reflux, the effective circulating blood volume of the body is then insufficient, resulting in hypotension [5, 56]. In previous studies, a U-shaped association was observed between pre-dialysis SBP and clinical outcomes among patients on dialysis [57, 58]. Patients with hypotension before dialysis are more likely to have IDH due to insufficient capacity or cardiovascular disease. Previous studies have demonstrated that higher pre-dialysis blood pressure is associated with an increasing percentage of interdialytic weight gain and lower dialysis Kt/v in subjects undergoing conventional hemodialysis [59, 60]. In normal individuals, the heart rate fluctuates with respiration because of a higher degree of beat-to-beat variability. However, in patients prone to IDH, such activation is impaired in the late phase of dialysis, contributing to the development of IDH [61]. During dialysis, hypotension occurs easily when the blood volume decreases significantly by more than 15%, but the change in blood volume can only be calculated by a change in the hematocrit. Adjusting the dialysis scheme according to the change in hematocrit is beneficial in reducing the occurrence of IDH [62].

We also included some new variables in our models, such as the neutrophil, lymphocyte, monocyte, and eosinophil counts, and the ratio of lymphocytes, which might require more comprehensive data for verification. However, the processes of variable screening and feature ranking are reliable. In the feature selection process, we deleted each feature one by one from the test dataset and compared the prediction results with the reference prediction results of all features; thus, the parameters that we filtered out were reliable. Among the feature screening methods we adopted, Lasso screening showed a better performance than other methods.

The results show that our machine learning method can predict IDH in a variable range; among the methods used, random forest had the best performance (AUC = 0.812). We also validated the system using a test dataset to evaluate the model's performance. Our model was found to be robust. The selected features obtained using the feature selection method provided the best performance. Important features that affected the accuracy of machine learning predictions (such as random forest) were the pre-dialysis SBP, pre-dialysis diastolic blood pressure, heart rate, dry weight, and ultrafiltration capacity.

Compared with the prediction model after dialysis, the advantage of this model is that it makes the prediction early and the risk of IDH can be predicted before dialysis, providing opportunities for medical staff to take early

Table 4. The 5 best performing models

Models	AUC	Accuracy	Precision	Recall	F1 score
Random forest	0.8186	0.7482	0.7407	0.6805	0.7094
Gradient boosting	0.8179	0.7462	0.7359	0.683	0.7085
Logistic regression	0.8173	0.7433	0.7345	0.6756	0.7038
SGD	0.8118	0.7414	0.7348	0.6699	0.7008
LDA	0.8113	0.7395	0.7318	0.6693	0.6992

intervention measures and conducive to reducing the occurrence of IDH in the first hour of dialysis. The disadvantage is that the performance of this model is worse than that of the models predicting after initiation of dialysis at 2–4 h.

The IDH prediction ability of our model was not the best as compared with previous studies; however, the data were obtained from a real-world practice software system automatically, without extra effort, which might be feasible in clinical settings, especially in large dialysis facilities. Our system analyzed a variety of data processing methods, including missing value processing methods and feature screening methods and evaluated the impact of different machine learning algorithms on model prediction performance. The system can be improved with more precise prospective and standardized data. Many predictive models have not been applied in clinical practice [13]. To the best of our knowledge, there is currently no randomized controlled trial verification of IDH early warning models. The system we constructed has been embedded in dialysis software and used as a sub page, and its clinical impact on IDH will be verified through our randomized controlled trial (ChiCTR2100047186) in the future.

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Statement of Ethics

The study was approved by the Ethical Committee of the Sichuan Provincial People's Hospital (No. 2017-124). The study followed the *Declarations of Helsinki* and *Istanbul*. Written informed consent was obtained for participation in this study.

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contributions

Daqing Hong: conception or design, analysis and interpretation of data, providing intellectual content of critical importance to the work described.

Huan Chang: analysis and interpretation of data, providing intellectual content of critical importance to the work described.

Xin He: drafting the article or revising it, analysis and interpretation of data, providing intellectual content of critical importance to the work described.

Ya Zhan: analysis and interpretation of data, revision of the article.

Rongsheng Tong: conception or design, revision of the article, providing intellectual content of critical importance to the work described.

Xingwei Wu: analysis and interpretation of data, providing intellectual content of critical importance to the work described.

Guisen Li: conception or design, revision of the article, providing intellectual content of critical importance to the work described, final approval of the version to be published.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material. Further inquiries can be directed to the corresponding author.

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