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Predictive modeling of blood pressure during hemodialysis: a comparison of linear model, random forest, support vector regression, XGBoost, LASSO regression and ensemble method

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ABSTRACT

Background: Intradialytic hypotension (IDH) is commonly occurred and links to higher mortality among patients undergoing hemodialysis (HD). Its early prediction and prevention will dramatically improve the quality of life. However, predicting the occurrence of IDH clinically is not simple. The aims of this study are to develop an intelligent system with capability of predicting blood pressure (BP) during HD, and to further compare different machine learning algorithms for next systolic BP (SBP) prediction.

Methods: This study presented comprehensive comparisons among linear regression model, least absolute shrinkage and selection operator (LASSO), tree-based ensemble machine learning models (random forest [RF] and extreme gradient boosting [XGBoost]), and support vector regression to predict the BP during HD treatment based on 200 and 48 maintenance HD patients containing a total of 7,180 and 2,065 BP records for the training and test dataset, respectively. Ensemble method also was computed to obtain better predictive performance. We compared the developed models based on R^2, root mean square error (RMSE) and mean absolute error (MAE).

Results: We found that RF (R^2=0.95, RMSE=6.64, MAE=4.90) and XGBoost (R^2=1.00, RMSE=1.83, MAE=1.29) had comparable predictive performance on the training dataset. However, RF (R^2=0.49, RMSE=16.24, MAE=12.14) had more accurate than XGBoost (R^2=0.41, RMSE=17.65, MAE=13.47) on testing dataset. Among these models, the ensemble method (R^2=0.50, RMSE=16.01, MAE=11.97) had the best performance on testing dataset for next SBP prediction.

Conclusions: We compared five machine learning and an ensemble method for next SBP prediction. Among all studied algorithms, the RF and the ensemble method have the better predictive performance. The prediction models using ensemble method for intradialytic BP profiling may be able to assist the HD staff or physicians in individualized care and prompt intervention for patients' safety and improve care of HD patients.

1. Introduction

Intradialytic hypotension (IDH) is a major notable complication in patients on hemodialysis (HD). The incidence of IDH has been reported with a wide range, from 7.5% to 69% according to the diagnostic criteria used [1-5]. Risk factors associated with IDH, such as ischemic heart disease, cardiac arrhythmia, systolic or diastolic dysfunction of the heart, old age, excessive interdialytic weight

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gain, malnutrition, diabetes, autonomic dysfunction, severe anemia, as well as low predialytic blood pressure (BP), have been noted in previous studies [2,3,6-9]. There is currently, however, no consensus on the definition of IDH [10].

Of note, the link between IDH and unfavorable outcomes, including arrhythmia [9], myocardial infarction [9], cardiovascular morbidity and mortality [11-13], myocardial stunning [14], thrombosis of the vascular access [15] and an insufficient dose of dialysis [16] is evident. Furthermore, IDH has also been reported to be associated with white matter ischemia and brain atrophy among patients undergoing HD [17-19]. Recurrent IDH may also predispose patients to mesenteric ischemia and endotoxemia, which can then lead to the generation of proinflammatory cytokines, endothelial dysfunction and oxidative stress, thereby increasing the risk of cardiovascular disease [7]. IDH could accelerate the loss of residual renal function [1] and increase risk of volume overload [20]. Prediction and prevention of IDH could drastically improve the quality of life for maintenance HD patients, but it remains challenging to develop an ideal prediction model for IDH.

In clinical practice, BP is measured frequently during HD treatment for patients' safety. Managing a HD patient's BP is difficult due to significant fluctuations and variations pre-, intra- and post-dialysis, and predicting these intradialytic fluctuations in BP is challenging. Accordingly, the aim of this study is to develop an intelligent system of BP profiling and prediction during HD. In this study, machine learning algorithms were applied to build a warning system prior to the occurrence of IDH and comparing different machine learning methods for next systolic blood pressure (SBP) prediction.

2. Materials and Methods

2.1. Patients and measurement methods

The study was retrospectively conducted at an outpatient HD unit in a regional hospital in Taiwan between September 2018 and May 2019. The study protocols were approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(II)-20180189). Adult patients (>18 years) were eligible to be included if they carried out maintenance HD treatments thrice weekly. Each treatment period was lasting up to 4 hours. The settings for HD treatment of most patients included dialysate sodium concentration of 138 mmol/L, dialysate potassium concentration of 2.0 mmol/L, dialysate calcium concentration of 2.5 mmol/L, dialysate flow rate of 500 mL/min, and dialysate temperature of 36.5°C. During HD treatment, BP and pulse rate were taken by electronic sphygmomanometers from the beginning to the end of HD on a half-hourly basis and additionally according to clinical needs, such as patients' cramp or discomfort. At each BP check, concurrent HD settings including dialysate temperature, ultrafiltration (UF) rate, blood flow rate, total UF volume and dialysate sodium concentration were recorded. The dry weight was defined as the lowest tolerated postdialysis weight achieved by gradual change and iterative process which there are minimal signs or symptoms of either hypovelemia or hypervolemia [21].

The Vital Info Portal (VIP) gateway device as well as the digital healthcare system collected the patients' BP and pulse rate and corresponding HD recording. To manage the electronic medical records of each study patient, Structured Query Language was used and the Oracle database was used for data storage. Other clinical information such as demographics, anthropometric characteristics, co-morbidities, vascular access type, cardiothoracic ratio, cardiac medication, Kt/V, frequency of IDH, and laboratory tests were collected for every participant. The cardiothoracic ratio was defined as the ratio of the transverse diameter of the cardiac shadow to the transverse diameter of the chest on chest radiographs. Kt/V was evaluated based on the Daugirdas formula to assess the adequacy of HD treatment [22]. The definition of IDH was based on predialysis SBP – minimum intradialytic SBP ≥30 mmHg and minimum intradialytic SBP <90 mmHg [2].

2.2. Training and testing dataset

We obtained 248 patients from our complete dataset. To enrich the dataset, we computed "delta" variables, such as detla_conductivity, delta_UF, delta_temperature, etc, to describe the change of dialysis parameters by clinical nurses. An example for the formula was written as: $\text{detla\_conductivity}_i = \text{conductivity}_i - \text{conductivity}_{i-1}$ where i was the record times of a patient. It was because that we assumed the doctors and nurses took certain actions to change HD settings would lead to BP change. We included the first SBP record which was measured before starting HD treatment as the baseline. In addition, we considered the previous HD status, such as previous SBP, previous dialysis temperature, etc., as "previous variables" to estimate the prediction of the following BP since the previous information influence the BP change as well. Furthermore, the average information for last HD session was also considered as the possible features to estimate the BP change. Several "mean variables" for last HD session were computed. The distributions for these variables are shown in Table 1. The data set was randomly partitioned into a training set of 200 patients and a testing set of 48 patients.

Training set: The final training set contained 200 patients with 7,180 BP records in which the incomplete or missing HD data were excluded. Testing set: The remaining 48 patients with 2,065 were served as a testing dataset for testing.

2.3. Statistical analysis

We modeled the next SBP value prediction using five machine learning methods, such as multiple linear regression, random forest regression, extreme gradient boosting (XGBoost), support vector regression and least absolute shrinkage and selection operator (LASSO) regression. All analysis was conducted with statistical package R version 3.5.1.

2.4. Multiple linear regression

In multiple linear regression, we want to map the relationship between a dependent variable, SBP, and explanatory variables. Including demographic variables, dialysis setting variables, delta variables, previous variables and mean variables. This result in a multiple regression model which was defined as: $\text{SBP} = \beta_0 + \sum_{k=1}^{K} \beta_k x_k + \varepsilon_k$

2.5. Random forest regression

The random forest algorithm is an extension of the decision tree algorithm, in which decision trees are combined and each decision tree is independently trained [23]. The training procedure was employed as follows: (1) from the training dataset, a bootstrap sample was drawn as a randomized subset; (2) each individual tree was grown using the randomized subset of predictor variables. Each tree model $f(x_i)$ was defined as $y_i = f(x_i) + \varepsilon_i$. The trees were grown to the largest extent possible without pruning; (3) repeat the step (2) until the number of trees was grown. Then the predicted results were aggregated by averaging them.

The package 'randomForest' version 4.6.14 was used with the number of parameters set at mtry=9; ntree=200; nodesize=5.

Table 1
Characteristics of the patients in training and testing dataset

	Training dataset	Testing dataset
Number of study patients	200	48
Number of SBP records	7180	2065
Age (years)	62.9 ± 11.6	60.9 ± 12.6
Men	97 (48.5%)	25 (52.1%)
Diabetes mellitus	91 (45.5%)	16 (33.3%)
Cardiovascular disease	33 (16.5%)	15 (31.3%)
Hypertension	109 (54.5%)	30 (62.5%)
SBP (mmHg)	130.0 ± 26.3	133.9 ± 22.4
UF goal (L)[a]	2.96 ± 1.03	3.19 ± 0.83
Dry weight (kg)[b]	58.4 ± 10.2	58.7 ± 12.6
Body temperature (°C)	36.2 ± 0.4	36.2 ± 0.4
Dialysis duration (years)	9.87 ± 7.11	9.02 ± 5.64
Blood flow (mL/min)	260.0 ± 61.7	267.7 ± 63.9
Albumin (g/dL)	3.95 ± 0.23	4.06 ± 0.28
Hemoglobin (g/dL)	10.4 ± 1.21	10.35 ± 1.08
Kt/V (Daugirdas)	1.61 ± 0.23	1.66 ± 0.25
Cardiothoracic ratio	0.51 ± 0.06	0.48 ± 0.04
AV fistula	185 (92.5%)	41 (85.4%)
AV graft	15 (7.5%)	7 (14.6%)
ACE inhibitors or ARBs use	34 (17.0%)	7 (14.6%)
Beta-blockers use	44 (22.0%)	9 (18.8%)
Calcium channel blockers use	42 (21.0%)	13 (27.1%)
Aspirin use	20 (10.0%)	7 (14.6%)
UF rate (L/hr)	0.61 ± 0.39	0.65 ± 0.38
UF/dry weight (%)	2.80 ± 1.80	2.88 ± 1.85
Dialysate calcium concentration (mmol/L)	2.55 ± 0.15	2.51 ± 0.08
Frequency of IDH	154 (2.1%)	25 (1.2%)
Previous SBP (mmHg)	132.9 ± 27.2	137.1 ± 22.3
Previous time (min)	127.6 ± 46.7	126.3 ± 49.0
Previous dialysis temperature (°C)	36.3 ± 0.5	36.3 ± 0.6
Previous UF rate (L/hr)	0.72 ± 0.34	0.79 ± 0.30
Previous dialysate conductivity (mS/cm) [c]	14.0 ± 0.11	14.0 ± 0.1
Previous blood flow (mL/min)	273.4 ± 36.4	281.5 ± 38.6
Previous total UF (L)	1.71 ± 0.85	1.82 ± 0.83
Δ_1 Elapsed time of HD (min)	46.7 ± 28.9	46.4 ± 29.5
Δ_2 Elapsed time of HD (min)	52.5 ± 33.0	51.1 ± 31.6
Δ_2 SBP (mmHg)	-3.9± 20.9	-2.3 ± 18.7
Δ_2 UF rate (L/hr)	-0.04 ± 0.27	-0.03 ± 0.26
Δ_2 Dialysis temperature (°C)	0.02 ± 0.27	0.00 ± 0.30
Δ_2 Dialysate conductivity (mS/cm)	0.01 ± 0.10	0.01 ± 0.11
Δ_2 Blood flow (mL/min)	1.95 ± 45.19	2.30 ± 39.07
Body weight before HD (kg)	62.0 ± 10.9	62.5 ± 13.3
Previous DBP (mmHg)	70.4 ± 15.0	71.2 ± 12.5
Previous pulse (beat/min)	74.5 ± 12.3	75.4 ± 12.0
Previous venous (mmHg)	133.4 ± 36.3	138.1 ± 38.2
Previous dialysate flow (mL/min)	499.4 ± 37.6	508.5 ± 59.0
Δ_2 Total UF (L)	0.70 ± 0.55	0.73 ± 0.53
Δ_2 DBP (mmHg)	-1.27 ± 10.95	-0.82 ± 9.34
Δ_2 Pulse (beat/min)	-0.23 ± 8.77	-0.55 ± 8.20
Δ_2 Venous (mmHg)	3.68 ± 27.51	4.54 ± 28.08
Δ_2 Previous dialysate flow (mL/min)	0.42 ± 23.72	1.43 ± 29.58
Mean SBP of last HD session (mmHg)	134.2 ± 23.2	137.6 ± 18.6
Mean DBP of last HD session (mmHg)	70.8 ± 13.1	71.5 ± 11.2
Mean UF of last HD session (kg)	0.65 ± 0.32	0.71 ± 0.29
Mean body temperature of last HD session (°C)	36.2± 0.4	36.2 ± 0.4
Mean venous pressure of last HD session (mmHg)	127.9 ± 38.5	132.6 ± 39.2
Mean dialysate conductivity of last HD session (mS/cm)	14.0 ± 0.2	14.0 ± 0.3
Mean dialysate flow of last HD session (mL/min)	498.9 ± 35.1	508.5 ± 55.9
Mean dialysate temperature of last HD session (°C)	36.3 ± 0.5	36.3 ± 0.5
Mean pulse of last HD session (beat/min)	75.0 ± 11.3	76.3 ± 10.8
First SBP record (mmHg)	139.4 ± 26.3	139. 8 ± 21.6

Values are expressed as means ± standard deviations (SD) for continuous data.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HD, hemodialysis; UF, ultrafiltration; AV, arteriovenous; ACE, angiotensin- converting enzyme; ARB, angiotensin receptor blocker; IDH, intradialytic hypotension.
* $\Delta_1 = t_i - t_{i-1}$; $\Delta_2 = t_{i-1} - t_{i-2}$.
UF goal [a]: the setting amount of fluid removal to achieve dry weight in each HD session.
Dry weight (kg)[b]: goal of body weight without fluid overload or hypovolemia.
Previous dialysate conductivity (mS/cm)[c]: a parameter of sodium concentration in dialysate

2.6. Extreme gradient boosting

The XGBoost model uses a gradient boosting framework and is also a decision-tree-based ensemble method. As the tree structure, f(x), the final prediction was calculated by summing up the scores across all leaves and this can be expressed as $\hat{y}_i = \sum_{j=1}^{N} f_j(x_i)$.The XGBoost makes improvement on objective optimization function which is to optimize the loss function and complexity punishment. We denoted the loss function and complexity punishment as $\sum_{i=1}^{n} l(y_i, \hat{y}_i)$ and $\sum_{k}^{k} \Omega(f_k)$, respectively.

For the XGBoost, the package 'xgboost' version 0.71.2 was used for which we set each parameter was max_depth=9, eta=0.2863 and gamma=0.0917.

2.7. Support vector regression (SVR)

SVR is one of the applications of Support-vector Machine (SVM). SVM constructs a hyperplane in a high-dimensional space, which can be used for classification and regression. Given the training data {(x_i, y_i), i = 1,2, . . . n}, where x was the independent variables as the independent variables in the multiple linear regression and y was SBP as well. The SVR developed an optimal function f(x) in which the Lagrange multipliers were converged.

$$f(x) = \sum_{i=1}^{N} \left(\alpha_i - \alpha_i^*\right) K\left(x_i, x_j\right) + b,$$

Where α_i and α_i^* were the Lagrange multipliers, b was a constant and K was the kernel function. In this study, we built the SVR model by 'e1071' package with default parameters.

2.8. Least absolute shrinkage and selection operator

We also applied LASSO regression (least absolute shrinkage and selection operator) which is a linear model with regularization. LASSO is the technique to reduce model complexity and avoid over-fitting in prediction model. We selected the β_j parameters to minimize the residual sum of squares: $\sum_{i=1}^{n} (\beta_0 + \sum_{k=j}^{K} \beta_k x_{k,i} - y_i)^2$,

In LASSO regression, we computed λ subject to minimize the residual sum of squares: $\sum_{i=1}^{n} (\beta_0 + \sum_{k=1}^{K} \beta_k x_{k,i} - y_i)^2 + \lambda \sum_{k=1}^{k} \beta_k$.

2.9. Statistical result

Continuous variables are presented as mean ± SD and categorical variables as absolute frequencies and percentages (n, %). R^2 was applied to indicate how a model explains the variation in the dependent variables. The root mean square error (RMSE) and mean absolute error (MAE) were reported to measure the prediction error.

$$\mathrm{RMSE} = \sqrt{\sum_{i=1}^{n} \frac{\left(y_i - \hat{y}_i\right)^2}{n}}$$

$$\mathrm{MAE} = \sum_{i=1}^{n} \frac{\left|y_i - \hat{y}\right|}{n}$$

3. Results

In this study, 200 and 48 maintenance HD patients containing a total of 7,180 and 2,065 BP records were collected in the training and test dataset, respectively. Among the individuals included in training dataset, the mean age was 62.9 ± 11.6 years, 48.5% were male, 45.5% were diabetic, and the mean dry body weight was 58.4 ± 10.2 kilograms. The summary of demographic features and HD records is shown in Table 1.

Table 2
Comparison of models on training and testing datasets.

Model	Training dataset			Testing dataset		
	R^2	RMSE	MAE	R^2	RMSE	MAE
Linear model	0.59	16.98	12.90	0.48	16.39	12.23
Random forest	0.95	6.64	4.90	0.49	16.24	12.14
XGBoost	1.00	1.83	1.29	0.41	17.65	13.47
SVR	0.78	12.58	8.57	0.44	17.17	12.99
LASSO	0.60	16.92	12.87	0.48	16.33	12.16
Ensemble	0.86	10.53	7.84	0.50	16.01	11.97

Abbreviations: RMSE, root mean square Error; MAE, mean absolute error, XGBoost, Extreme Gradient Boosting; SVR, support vector regression; LASSO, least absolute shrinkage and selection operator.

Table 2 presents R^2, RMSE and MAE of linear model, random forest, XGBoost, SVR, LASSO and ensemble method on training and testing datasets for predicting SBP. RMSE and MAE on the training dataset show the goodness-of-fit of the developed models and RMSE and MAE on the testing dataset show the performance of the developed models. The ensemble prediction value was calculated by averaging the predictions from the above-mentioned algorithms. Linear model has the highest RMSE. However, we did not apply feature selection method in linear model. Therefore, we adopt LASSO regression with regularization. Generally, the random forest algorithm has better performance across training and test datasets. However, XGBoost has the lowest MAE in training dataset (MAE=1.29), but has the highest RMSE and MAE testing dataset. It means that XGBoost may encounter more serious overfitting problem than other algorithms. The random forest algorithm has the lowest MAE in testing dataset compared with other algorithms except ensemble method. Furthermore, we averaged prediction of above algorithms as ensemble prediction, we found the lowest MAE in testing dataset were calculated by ensemble method.

Total data included 57 variables and Pearson coefficients between SBP and other variables are demonstrated in Figure 1. We only presented top 10 most correlated variables in both positive and negative correlation and we found the top five most correlated with SBP is the previous SBP record, the mean SBP of last HD session, first SBP record, the previous diastolic blood pressure (DBP) and the mean of DBP of last HD session. The top five variables were all positive correlation. Besides, the previous HD time, Kt/V, the previous total UF and the previous pulse rate were negative correlated with SBP. However, the demographic features are less correlated with SBP than physiological and hemodialysis parameters.

4. Discussion

In this study, we compared five machine learning models and an ensemble method to predict SBP. Even though XGBoost had the highest R^2 and smallest RMSE and MAE for the training dataset, the RMSE and MAE for the testing dataset were the most important for the purpose of constructing a predictive model as an early warning system for use in clinical practice. Among these models, the ensemble method (R^2=0.50, RMSE=16.01, MAE=11.97) had the best performance on testing dataset for next SBP prediction.

The first important finding of this study is the performance of machine learning algorithms for prediction of intradialytic BP. Our results demonstrated that the random forest algorithm had lower RMSE and MAE values in the testing dataset (16.24 and 12.14, respectively) compared to the RMSE and MAE of XGBoost (17.65 and 13.47, respectively). The SVR method had an unsatisfied perfor-

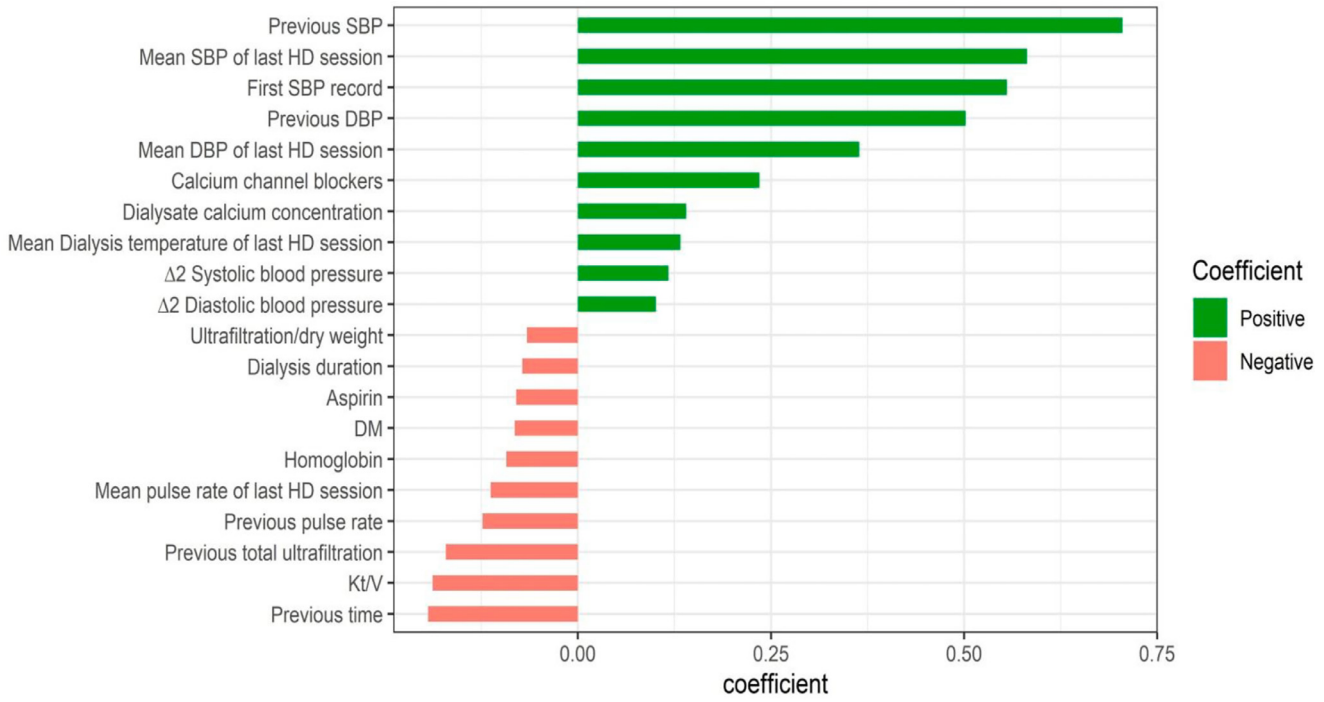

Figure 1. The correlation coefficients between systolic blood pressure and variables.

mance with RMSE and MAE values of 17.17 and 12.99, respectively. Linear regression model and LASSO had similar RMSE and MAE values to the random forest model, although ensembles of these algorithms slightly improved the performance of the models. In this study, it is interesting that the linear model had a similar performance to the LASSO method which decreased the coefficients of collinear covariates towards each other. It is possible that only a few important features were included in both models. Even though we included many potential explanatory variables, the R^2 for these models was only moderate. Furthermore, the performance of these models may be enhanced by incorporating laboratory indexes of study patients.

Even though the scientific technology and computer industry drastically progress in the recent decades, prediction of IDH and changes in BP is still currently challenging for clinicians in HD patients. Previous studies have reported that dialysis machine-related parameters, such as calcium and sodium concentrations in the dialysate and the dialysate temperature, can play important roles affecting BP during HD [24-26]. However, in our machine learning models, the top five most highly correlated variables (previous SBP, mean SBP of the last HD session, first SBP reading, previous DBP reading and mean DBP in the last HD session) did not include any dialysis machine-related parameter. Thus, HD machine-related parameter may affect BP during HD, but not as relevant as the level of hemodynamic parameters affect.

Of note, the most important predictor of the next SBP reading during HD in this study was the level of the previous SBP, followed by mean SBP in the last HD session, first SBP reading, previous DBP reading and mean DBP in the last HD session. Rapid plasma osmolalilty changes [27], body fluid removal [9,28], electrolyte imbalance [29,30], and myocardial stunning [31] are interacting pivotal elements of hemodynamic instability during HD session. IDH is potentially life-threatening, and preventive strategies for high-risk patients must be developed. These strategies include avoidance of aggressive UF volume and UF rate, UF and sodium modeling to achieve the dry weights, controlling interdialytic weight gain, cessation of long-acting vasodilators and pre-dialysis antihypertensive drugs, and not eating during HD treatments [32,33]. Moreover, surveillance of cardiac etiologies of IDH, such as cardiac arrhythmia, impaired systolic function, and coronary artery disease, should also be done. Modifying the routine HD schedule to longer treatment duration and/or frequent HD treatments per week may minimize the risk of IDH as well [34]. However, this is dependent on whether the patient can tolerate the treatment. Chronic HD patients were generally unwilling to have extended or longer treatment duration [35]. The balance of the consequences of IDH and patients' will could be possibly achieved in the future, though this kind of machine-learning model to prediction of BP changes during HD.

There are several limitations to this study. First, this is a retrospective study, therefore it was difficult to elucidate the effects of all clinical variables on intradialytic BP. In fact, the intelligent system developed in this study showed an impressive accuracy in predicting intradialytic changes in SBP. Further studies, however, are needed to validate this intelligent system in more large-scaled HD patient population. Second, we could not assess the long-term impact of anti-hypertension medications on intradialytic BP. In this case, the medication may have had an effect on an HD session even if it was not taken on the day of dialysis. Third, we lacked data in regard to interventions and symptoms that may alter the BP, and these factors may confound our associations. Even though we adjusted carefully for clinically relevant covariates and certain established risk factors for IDH, residual confounding and/or unmeasured confounders may still exist. Fourth, this algorithm did not consider extracellular fluid status, bioimpedance information and cardiac performance of patients. Further studies are warranted to include these important factors and develop more individualized algorithm. Moreover, this retrospective study does not indicate that in a prospective way the predictive value of this model will remain accurate and will improve clinical outcome. This concept deserves further studies including refinement in modeling approach and prospective testing in real life. Finally, we used data from a single center to develop our prediction models, and thus our results may not be directly applicable to other patient groups.

However, as the model performed well in the prediction for new patients, suggesting that it should be probably applied in other HD centers.

5. Conclusion

IDH is associated with significant signs and symptoms that require interventions. The frequency of IDH also has significant prognostic implications. The prediction models using ensemble method for intradialytic BP profiling may be able to assist the dialysis staff or physicians in individualized care and providing prompt intervention for patients' safety and improvement of patient care . The application of an intelligent early warning system of BP prediction might be helpful for clinical decision-making, patients' safety, and reduction in frequency of IDH. Furthermore, the use of this kind of prediction model to achieve BP-targeted outcomes and provide insights into how to reduce the occurrence of intradialytic BP variability and its associated co-morbidities are worthy of further investigations.

Authors' Contributions

Research idea and study design: Jiun-Chi Huang, Szu-Chia Chen, Chao-Hung Kuo

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Statistical analysis: Jiun-Chi Huang, Yi-Chun Tsai, Pei-Yu Wu

Supervision or mentorship: Jeng-Fung Hung, Szu-Chia Chen, Chao-Hung Kuo

All authors contributed important intellectual content during manuscript drafting or revision, and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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