

Received February 29, 2020, accepted April 14, 2020, date of publication April 20, 2020, date of current version May 15, 2020.

Digital Object Identifier 10.1109/ACCESS.2020.2988993

Deep Learning for Intradialytic Hypotension Prediction in Hemodialysis Patients

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This work was supported by the Ministry of Science and Technology, Taiwan, under Grant 107-2221-E-214-013- and Grant 106-2221-E-992-327-MY2.

ABSTRACT Intradialytic hypotension is a common problem during hemodialysis treatment. Despite several clinical variables have been authenticated for associations during dialysis session, the interaction effects between variables has not yet been presented. Our study aimed to investigate clinical factors associated with intradialytic hypotension by deep learning. A total of 279 participants with 780 hemodialysis sessions on an outpatient in a hospital-facilitated hemodialysis center were enrolled in March 2018. Associations between clinical factors and intradialytic hypotension were determined using linear regression method and deep neural network. A full-adjusted model indicated that intradialytic hypotension is positively associated with body mass index (Beta = 0.17, $p = 0.028$), hypertension comorbidity (Beta = 0.17, $p = 0.008$), and ultrafiltration amount (Beta = 0.31, $p < 0.001$), and is inversely associated with the ultrafiltration rate in a hemodialysis session (Beta = -0.30, $p = 0.001$). The 4-factor locus obtained by the deep neural network reached the maximum performance metrics evaluation (accuracy = 64.97 ± 0.94 ; true positive rate = 87.97 ± 2.73 ; positive predictive value = 66.74 ± 0.98 ; Matthews correlation coefficient = 0.19 ± 0.03). The prediction model obtained by the deep learning scheme could be a potential tool for the management of intradialytic hypotension.


INDEX TERMS Hemodialysis, deep learning, intradialytic hypotension.

I. INTRODUCTION

Intradialytic hypotension (IDH) is not an uncommon event that occurs during a hemodialysis (HD) procedure. The incidence is reported approximately 5% to 30% during HD treatment [1]–[4]. IDH is commonly defined as a decrease in the systolic blood pressure by ≥ 20 mmHg or in mean arterial pressure by ≥ 10 mmHg [5], [6]. The pathophysiological mechanisms of IDH are complex. Two components have been discussed since past few years. First, an imbalance between central hypovolemia and the adequacy of hemodynamic responses. In end-stage kidney disease, patients commonly manifest autonomic and baroreceptor dysfunction and

disturbed cardiac function. Second, uncompensated plasma refilling occurs during the ultrafiltration procedure of HD. During HD, the ultrafiltration procedure removes the fluid from the vascular space and replaces the fluid in the interstitial space (plasma refilling). The rate of ultrafiltration during HD influences the rate of plasma refilling. When the amount of ultrafiltration exceeds the plasma refilling amount, IDH becomes an unavoidable event. Clinically, there are several diseases and circumstances apt to develop IDH during an HD procedure, namely diabetes mellitus, cardiac disease, autonomic neuropathy, severe liver disease, antihypertensive etc [7].

Deep learning has been proved to be excellent for solving intricate problems and mathematical structures, and can be applied to a wide range of sciences, such as image/speech

The associate editor coordinating the review of this manuscript and approving it for publication was Danilo Pelusi .

recognition, financial technology, computational biology and bioinformatics [8]. Several deep learning architectures have been categorized such as: deep neural networks (DNN), convolutional neural networks, recurrent neural networks, and other emergent or hybrid architectures [9]. The deep learning model uses training data to discover underlying patterns and helps in constructing models, and fitting the best model for prediction. Those models can be applied widely to bioinformatics, such as biomedical text recognition, biomedical imaging, biomedical signal processing, genomics, and gene expression [9]. Deep learning is an emerging technique for renal study. Several literatures have revealed that deep learning has an advantage of better performance in achieving breakthroughs in various fields [10]–[12].

Multifactor dimensionality reduction (MDR) [13] is a well-known nonparametric and model-free approach that was developed for interaction effect investigation in case-control studies. MDR can be used to characterize high order interaction effects on risk of multi-factor complex diseases. Many theoretical and empirical studies demonstrated that MDR has reasonable power to identify interaction among multi-factors in relatively small samples [13], [14]. MDR has been successfully applied to detect interaction effect in hypertension [15], coronary artery disease [16] and breast cancer [17]. MDR have been improved and applied in various biomedicine topic recently [16], [18]–[22]. The interaction analysis of this study is inspired from MDR that pooled the multi-level characteristics of clinical factors into high-risk and low-risk groups to identify high-risk interaction model of rapid IDH.

In the present study, we aimed to find the vulnerable variables, namely, demographics, comorbidities, laboratory parameters, vascular access parameters, reference values of HD machines during an event of IDH, components of dialyzers and drugs, by using deep neural network. The purpose was an attempt to find the significance of individual variables in the occurrence of rapid IDH. Thus, optimal measures were expected to be applied in individual cases to prevent rapid IDH.

II. METHODS

A. PARTICIPANTS

The patients who were undergoing HD regularly on an out-patient basis at the Kaohsiung Chang Gung Memorial Hospital in Taiwan were enrolled for the investigation. The adult patients with IDH during the HD procedure were recruited. IDH was defined as the decrease in the systolic blood pressure by >20 mmHg during the HD procedure. The included patients were followed-up from 1st March 2018 to 31st March 2018. All the patients were undergoing HD every week. The protocol for the study was approved by the Committee of Human Research at Kaohsiung Chang Gung Memorial Hospital (IRB no: 201800595B0) for a retrospective review of the medical data and waived the informed consent for institutional review board (IRB) regulation in the hospital.

B. DEMOGRAPHIC DATA AND CLINICAL VARIABLES IN HEMODIALYSIS SESSION

Data collection was performed for the demographic information including age, gender, dry weight, BMI, etiologies of end-stage kidney disease, comorbidities, and drug history. The notes related to the clinical variables of the HD sessions were collected, including HD vintage, frequency of HD per week, duration (years) of each HD session, UF amount per hour (L/hour) and UF rate (L/hour) during each HD session, UF coefficient during the IDH event, blood flow rate (mL/min), types of vascular access, components of dialyzers, and occurrence time of IDH. The membrane materials of the dialyzers were cellulose acetate (170G, FB210U), polysulfone (FXCor1000, FXCor60, PS-2.0W, PS-2.3W), polyether sulfone (EL-21H, EL-25H), and polymethylmethacrylate (BG2.1U). The dialysate flow was constant in all the HD sessions (500 mL/min). The temperature of the dialysate was 37 °C; the calcium (Ca) concentration of the dialysate was 3.0 mEq/L and the bicarbonate concentration was 34 mEq/L.

C. LABORATORY DATA

Baseline laboratory values for the blood analysis were measured in the midweek (on Wednesday or Thursday) via a venous port prior to the HD session, following an overnight fasting. The parameters included hemoglobin (Hb), albumin, blood urea nitrogen (BUN), creatinine (Cr), Ca, phosphate (P), sodium (Na), potassium (K), ferritin, and intact parathyroid hormone (iPTH) levels; the fractional removal of urea per dialysis treatment (Kt/V); urea reduction ratio (URR); normalized protein catabolic rate (nPCR); and cardiothoracic ratio estimated by the chest x-ray examination. Detailed information about the measurements such as Kt/V urea, URR, nPCR, and cardiothoracic ratio have been described in our previous article [23].

D. STATISTICAL ANALYSES

The distribution of the continuous factors was summarized as mean \pm standard deviation or median and interquartile range, as appropriate; and the categorical factors were summarized in terms of frequency and percentage. Linear regression analyses were performed to demonstrate the interaction between the associated factors and IDH. The full-adjusted multivariate model considered all the associated variables as covariates. A *p*-value less than 0.05 was considered as statistically significant. A cumulative incidence risk of IDH was visualized by using the Kaplan-Meier curve. All the statistical analyses were performed using the Stata 11.0.

E. DATA PREPROCESSING

This study included patients who were undergoing the hemodialysis treatment for 4 hours, which reported the occurrence time of IDH. We classified the patients into 2 groups; The patients are divided into low-and high-risk group according to their IDH occurrence time. The high-risk group is defined as the patients with rapid IDH (occurrence time less

than 120 minutes), while the low-risk group is defined as the patients with IDH occurrence time greater than 120 minutes. The baseline characteristics of the patients were pre-processed by using the standardization, which transferred the values of each factor from the center of the mean- and component-wise scale to the unit variance. Here, we used the data of all the factors to train each classifier model and test its performance; then, the p -value <0.2 for the factors of the full-adjusted model were selected for a factor-interaction testing.

F. DEEP NEURAL NETWORK MODELS

Figure 1 illustrates the progress of 8 steps in implementing a deep learning scheme for the prediction of rapid IDH. A grid search method was used to obtain the optimal hyper-parameters for deep neural network (DNN) model. In step 1, a DNN model was implemented in this study; we used a training set and a testing set with a k -fold cross-validation to train and test the DNN model and factors selection model. The data were randomly divided into k equally-sized subsets. In step 2, m dimension (multifactor) of input data set for the prediction model was selected from the pool of all factors, where n factors have C_m^n possible combinations with m multifactor interaction. In step 3, the input data set was split into a training set and a validation set in a 8:2 ratio for the DNN prediction model creation. In step 4, all the possible combinations of m multifactor interaction were trained and validated, and the best model with the validated identification accuracy was obtained. In step 5, the best prediction model of m multifactor interaction combinations was created, and then its performance was evaluated by the testing set. Finally, the k -fold cross-validation was repeated k times, the prediction accuracies were averaged, and a cross-validation consistency was obtained. Step 6, scatter plot matrix was plotted to observe the correlations between each factors. In step 7, receiver operating characteristic (ROC) curve was used to determine the best threshold in individual factor, then the continuous data were transformed into categorical data according to best threshold calculated by Youden index. Finally, the best multifactor model derived from DNN was used to analysis the cumulative risk effect based on the multi-factor interaction model. Details interpretation for DNN and cross-validation are shown in Supplementary file.

III. RESULTS

A. ASSOCIATION BETWEEN RAPID IDH AND CLINICAL FACTORS

Total 279 patients with the mean aged of 63.04 years were enrolled and the clinical characteristics of all patients are summarized in Table 1. There were 136 (48.7%) male and 143 (51.3%) female patients. The cumulative incidence risk of IDH is summarized using a cumulative curve in Figure 2. The IDH was more likely to occur 30 minutes after HD treatment. Table 2 demonstrates the association between the IDH and clinical factors. The univariate analysis indicated that IDH is positively correlated with the hypertension comorbidity

TABLE 1. Baseline Characteristics.

Variables	Mean	SD
Age (year)	63.04	± 11.8
BMI (kg/m ²)	23.39	± 4.11
Body weight (dry) (kg)	61.10	± 12.99
Gender (n, %)		
Male	136	48.7
Female	143	51.3
Etiology in ESRD (n, %)		
A (Renal Parenchymal Diseases)	80	28.7
B (Systemic Diseases)	168	60.2
E (Hereditary Diseases)	2	0.7
F (Other Causes of Renal Failure)	3	1.1
G (Renal Failure, Cause Unknown)	26	9.3
Comorbidity (n, %)		
DM	111	39.8
Hypertension	44	15.8
Others (Cirrhosis, CAD)	6	2.2
Antihypertensive	63	22.6
Dialyzer (n, %)		
170G	29	10.4
BG2.1U	45	16.1
EL-21H	53	19.0
EL-25H	52	18.6
FB-210U	56	20.1
FXCor1000	22	7.9
FXCor60	6	2.2
PS-2.0W	14	5.0
PS-2.3W	2	0.7
Vascular access (n, %)		
Fistula	231	82.8
Gore-Tex	23	8.2
Catheter	25	9.0
Blood flow rate (mL/min)	250	230-270
UF coefficient (mL/h/mmHg)	76	41.7-82
UF amount (% dry weight)	3.56	± 1.58
UF rate (L/hour)	0.74	± 0.28
MAP in beginning (mmHg)	99.67	89.67-112.33
MAP in hypotension (mmHg)	84.67	72.33-94.67
SBP beginning (mmHg)	153	137-173
SBP in hypotension (mmHg)	124	109-140
SBP reduction from beginning (mmHg)	31.04	± 11.23
Occurrence time of hypotension (minutes)	102	63-141
Laboratory measurements		
Hb (g/dL)	10.53	± 1.08
Albumin (g/dL)	3.92	± 0.33
Ca (mg/dL)	9.51	± 0.89
P (mg/dL)	5.29	± 1.48
K (meq/L)	4.75	± 0.75
Na (meq/L)	135.11	± 3.35
Ferritin (ng/mL)	362.4	213.7-538
BUN (mg/dL)	73	58-88
Cr (mg/dL)	10.50	± 2.71
Kt/V urea	1.45	± 0.52
iPTH (pg/mL)	276.9	116.6-604.6
nPCR (g/kg/day)	1.17	± 0.45
URR (%)	0.70	± 0.3
CTR (%)	0.52	± 0.08

ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, Hb, hemoglobin; Ca, calcium; P, phosphate; K, potassium; Na, sodium; BUN, blood urea nitrogen; Cr, creatinine; iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; URR, urea reduction ratio; CTR, cardiothoracic ratio.

(Beta = 0.15, $p = 0.012$) and serum calcium (Ca) level (Beta = 0.13, $p = 0.033$), and is inversely correlated with the cardiothoracic ratio (Beta = -0.13, $p = 0.032$). The full-adjusted multivariate model indicated that IDH

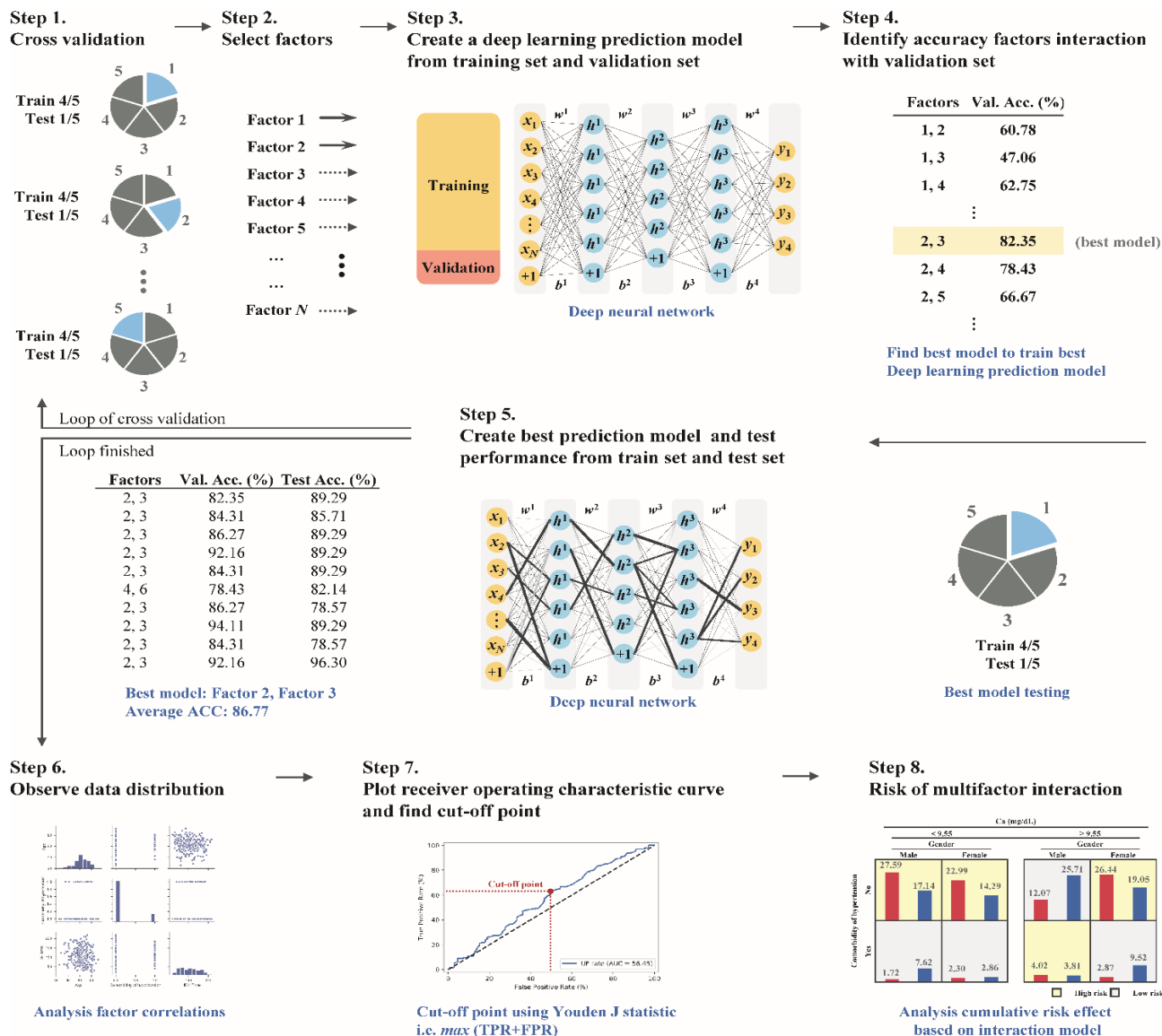


FIGURE 1. Overall factors of the interaction framework for the prediction of intradialytic hypotension using deep learning network. The best multi-factor combination model is determined by using deep neural networks, the validation accuracy (Val. Acc.) and test accuracy (Test Acc.) were estimated by 5-fold cross-validation (i.e. step 1 to step 5). The factor correlation and risk of multi-factor interaction are considered in step 6 to step 8.

is positively correlated with the body mass index (BMI) (Beta =0.17, $p =0.028$), hypertension comorbidity (Beta =0.17, $p =0.008$), and ultrafiltration (UF) amount (% dry weight, Beta =0.31, $p <0.001$), and is inversely correlated with the UF rate (Beta =-0.3, $p =0.001$).

B. PERFORMANCE COMPARISON BETWEEN PREDICTION MODELS

Several general classifiers were implemented as the prediction models, referring the scikit-learn library v0.19.1 [24] in Python language, namely, support vector machine (SVM), artificial neural network (ANN), random forest (RF), decision tree (DT), k-nearest neighbor (KNN), and naïve Bayes (NB). The performance metrics of binary classification

task were estimated from the complete feature set of each classifier by performing the 5-fold cross-validation on the dataset. The average ROC curve and area under the curve (AUC) score were plotted, as shown in Figure 3. We estimated the ROC by using a *sklearn.metrics* package in the scikit-learn library v0.19.1 [24]. The comparative analysis shows the DNN model could achieved better performance (AUC = 64.90 ± 3.11) than others models. The ROC for DNN model (red line) is approximately 10% superior to the second highest results achieved by the RF model (dashed purple line). The comparative analysis showing that DNN model could obtain superior performance and high robustness in quantitative assessment compared to other models.

TABLE 2. Linear regression analysis.

Variables	Univariate		Full-adjusted Model	
	Beta	<i>p</i>	Beta	<i>P</i>
Age (year)	-0.08	0.159	-0.13	0.080
BMI (kg/m ²)	0.04	0.488	0.17	0.028
Gender, Male	-0.10	0.106	-0.11	0.158
Comorbidity				
DM	0.02	0.745	0.06	0.356
Hypertension	0.15	0.012	0.17	0.008
Antihypertensive	0.03	0.631	-0.02	0.700
Vascular access, Gore-Tex vs Fistula	-0.001	0.984	0.06	0.321
Vascular access, Catheter vs Fistula	-0.06	0.341	0.023	0.725
UF coefficient (mL/h/mmHg)	0.10	0.089	0.101	0.184
Blood flow rate (mL/min)	0.02	0.781	-0.1	0.207
UF amount (% dry weight)	0.08	0.159	0.31	<0.001
UF rate (L/hr)	-0.04	0.474	-0.3	0.001
MAP in beginning	0.05	0.449	-0.01	0.893
Laboratory measurements				
Hb (g/dL)	0.002	0.978	-0.02	0.738
Albumin (g/dL)	-0.04	0.523	-0.08	0.316
Ca (mg/dL)	0.13	0.033	0.12	0.062
P (mg/dL)	-0.01	0.847	-0.07	0.285
K (meq/L)	-0.01	0.916	0.04	0.551
Na (meq/L)	-0.03	0.566	-0.05	0.474
Ferritin (ng/mL)	-0.08	0.193	-0.032	0.618
BUN (mg/dL)	-0.04	0.558	-0.06	0.366
Cr (mg/dL)	0.07	0.218	0.02	0.833
Kt/V urea	0.00	0.961	-0.05	0.598
iPTH (pg/mL)	0.07	0.24	0.07	0.293
URR (%)	0.03	0.646	0.02	0.769
CTR (%)	-0.13	0.032	-0.12	0.077

p-values for categorical variables were calculated by χ^2 test, and continuous variables were calculated by independent two samples. *p*-values < 0.05 are highlighted in bold for each factor. BMI, body mass index; DM, diabetes mellitus; UF: ultrafiltration; MAP: mean arterial pressure; SBP, systolic blood pressure; Hb, hemoglobin; Ca, calcium; P, phosphate; K, potassium; Na, sodium; BUN, blood urea nitrogen; Cr, creatinine; iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; URR, urea reduction ratio; CTR, cardiothoracic ratio.

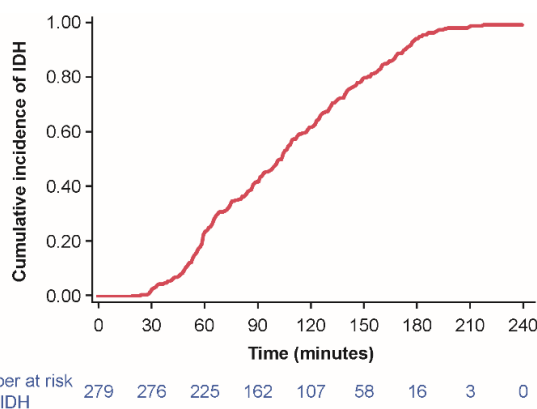


FIGURE 2. Kaplan-Meier plot for cumulative incidence of IDH. Number at risk indicates the number of patients at risk for IDH occurrence at each time point are given. IDH, intradialytic hypotension.

C. MULTI-FACTORS INTERACTION MODEL BASED ON DNN MODEL

We estimated the performance in terms of accuracy (*ACC*), sensitivity (e.g. true positive rate, *TPR*), precision

(e.g. positive predictive value, *PPV*), and Matthews correlation coefficient (*MCC*), which were calculated as true positive (*TP*), true negative (*TN*), false positive (*FP*), and false negative (*FN*) values. Particularly, the terms *ACC*, *TPR* and *MCC* are calculated as:

$$ACC = \frac{TP + TN}{TP + FP + TN + FN} \tag{1}$$

$$TPR = \frac{TP}{TP + FN} \tag{2}$$

$$PPV = \frac{TP}{TP + FP} \tag{3}$$

$$MCC = \frac{(TP \times TN) - (FN \times FP)}{\sqrt{(TP + FN) \times (TN + FP) \times (TP + FP) \times (TN + FN)}} \tag{4}$$

Table 3 summarizes the performance of multi-factor interaction effects based on DNN model using 5-fold cross-validation and 100 evaluation cycles. The 4-factor locus revealed the maximum values after the performance metrics evaluation [*ACC* = 64.97 ± 0.94 (%); *TPR* = 87.97 ± 2.73(%); *PPV* = 66.74 ± 0.98 (%); and *MCC* = 0.19 ± 0.03].

TABLE 3. Summary results for multi-factor interaction effect based on DNN model.

Num.	Best model	ACC (%)	TPR (%)	PPV (%)	MCC
2	A-D	63.24 ± 1.18	91.54 ± 2.61	64.48 ± 0.70	0.13 ± 0.04
3	C-D-H	62.35 ± 1.96	87.55 ± 3.02	64.71 ± 1.30	0.11 ± 0.06
4	D-E-F-G	64.97 ± 0.94	87.97 ± 2.73	66.74 ± 0.98	0.19 ± 0.03
5	B-D-E-F-G	63.72 ± 1.32	85.15 ± 2.79	66.39 ± 1.06	0.17 ± 0.04
6	B-D-E-F-G-I	63.41 ± 1.27	83.98 ± 2.66	66.43 ± 1.08	0.16 ± 0.04
7	A-B-C-E-F-G-H	62.96 ± 2.00	80.96 ± 3.51	66.82 ± 1.20	0.16 ± 0.04

Num., number of factor; ACC, accuracy; TPR, true positive rate; PPV, positive predictive value; MCC, Matthews correlation coefficient; A, age; B, BMI; C, gender; D, comorbidity of hypertension; E, ultrafiltration coefficient; F, ultrafiltration amount; G, ultrafiltration rate; H, Ca; I, cardiothoracic ratio.

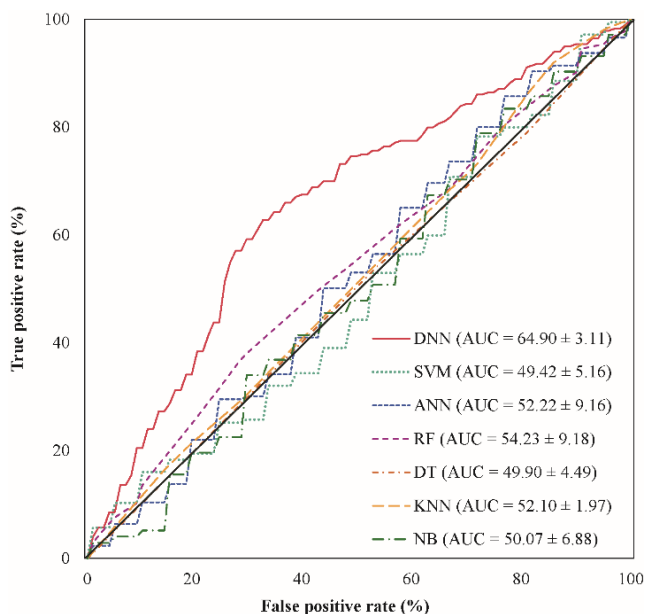


FIGURE 3. Receiver operating characteristic curves (ROC) and area under the curve (AUC) of the classifier models for the prediction of the occurrence of rapid IDH using 5-fold cross-validation test set. The comparison of performance between seven classifier using AUC of all factors. DNN, deep neural network; SVM, support vector machine; ANN, artificial neural network; RF, random forest; DT, decision tree; KNN, k-nearest neighbor; NB, naïve Bayes.

Although, the ACCs were only approximate to 65%, while the TPRs were generally high (above 85%) which indicate the multi-factor interaction model was highly sensitive in the prediction of rapid IDH. The highly associated interaction risk factors for rapid IDH including hypertension comorbidity, UF coefficient, UF rate, and UF amount.

D. CUMULATIVE RISK EFFECT BASED ON MULTI-FACTORS INTERACTION MODEL

The patients are divided into low-and high-risk group according to their IDH occurrence time. The high-risk group is defined as the patients with rapid IDH (occurrence time less than 120 minutes), while the low-risk group is defined as the patients with IDH occurrence time greater than 120 minutes. The scatter plot for all factors included 4-factor interaction model is summarized as a matrix in Figure S1. According to the matrices, the IDH occurrence time show no clearly

correlation with each individual factor. Thus, we used the ROC analysis to determine the best cut-off point of each factor according to Youden index for IDH low-and high-risk group in order to reduce the dimension complexity, and enable us to determine the characteristic which is highly associated with rapid IDH. The cut-off thresholds were calculated and transformed the continuous data into categorical for selected factors as shown in Table 4.

The summary of 2- to 7-factor combinations associated with high-low risk for IDH is presents in Figure S2-S7. In 2-factor interaction model, patients without hypotension in both age groups obtained higher risk in rapid IDH occurrence. In 3-factor interaction model, the patients with lower calcium level (< 9.55 mg/dL) and without hypertension, female patients with higher calcium level (≥ 9.55 mg/dL) and without hypertension, male patients with higher calcium level (≥ 9.55 mg/dL) and hypertension obtained higher risk in rapid IDH occurrence. In 4-factor interaction model, patients with lower UF amount (< 2.46% dry weight) and without hypertension, patients with lower UF amount (< 2.46% dry weight) and hypertension and higher UF coefficient (≥ 87.5 mL/h/mmHg) and higher UF rate (≥ 0.66 L/hour), patients with higher UF amount (≥ 2.46% dry weight) and without hypertension and higher UF rate (≥ 0.66 L/hour) and lower UF coefficient (< 87.5 mL/h/mmHg) were considered obtained higher risk in rapid IDH occurrence.

The cumulative risk performance in 2- to 7-factor is determine using ROC analysis and the results is summarized in Table S1 and Figure S8. The interaction model with cumulative risk consideration showed a better result compare to the individual risk factor estimation. The AUC showed a rising trend from 2- to 6-factor interaction model, and slightly reduced in 7-factor interaction model. We found the 4- to 6-factor interaction model all include four factors (UF amount, UF rate, UF coefficient and hypertension), while the 7-factor interaction model did not include hypertension comorbidity. In summary, the interaction model in 2- to 7-factor was obtained higher AUC than individual model.

IV. DISCUSSION

Present study demonstrated that DNN model could use as a potential tool in clinical practice for the prediction of rapid IDH. We examined the associations between several

TABLE 4. The cut-off thresholds and dichotomous performance in rapid IDH prediction using ROC analysis.

Factor	Original		Adjusted		Cut-off thresholds
	AUC (%)	95% CI	AUC (%)	95% CI	
Age	54.43	47.55-61.30	54.81	48.79-60.83	64.50
BMI	53.18	46.31-60.05	55.02	40.24-49.71	20.56
UF coefficient	56.98	49.93-64.03	57.18	37.43-48.21	87.50
UF amount	51.81	44.88-58.73	54.45	40.85-50.25	2.47
UF rate	56.45	49.40-63.50	56.85	50.85-62.85	0.66
Ca	57.77	50.86-64.67	56.35	50.33-62.37	9.55
CTR	55.55	48.62-62.48	57.57	51.68-63.46	0.53

BMI, body mass index; UF, ultrafiltration; Ca, calcium; CTR, cardiothoracic ratio; AUC, area under curve; 95% CI, 95% confidence interval.

clinical variables and IDH by 7 prediction models with AUCs approximately 65%. Although the AUCs did not reach a perfect standard, the clinical variables determined from the deep learning model were reasonable, as per the experiences in the clinical practice. We found that rapid IDH commonly occurred within the first 120 minutes after HD initiation. We hypothesized that the intravascular refilling would not be adequate when UF is applied during the dialysis during the HD sessions. However, we could not determine the definitive cause of this time-effect of the occurrence of IDH because of incomplete evaluation of the individual cardiopulmonary function. Nevertheless, this time-effect of IDH cannot be refuted based on the common clinical experiences. We also found that leading factors associated with the occurrence of IDH during the HD were the UF amount (% dry weight), UF rate, and hypertension comorbidity. The full-adjusted model revealed positive correlations between the occurrence of IDH during the HD sessions and the BMI, UF amount, and hypertension comorbidity. Accordingly, these results were compatible with the clinical experiences [25]–[29]. Several reports indicated the variability of blood volume in the HD sessions was related to IDH events [30]–[34]. However, use of blood volume monitoring-guided UF in the HD sessions did not reduce the rate of IDH events in one randomized crossover study [29]. We also cannot give the definitive reason for the correlation of the hypertension comorbidity. The supposed causes may include the use of antihypertensive during the pre-dialysis period, cardiac dysfunction related to the hypertension and potential undefined hypertension-related circumstances, etc [35], [36]. Nevertheless, this finding indicates the importance of being aware of the hypertension comorbidity during IDH management. The UF rate during the IDH event was inversely correlated with IDH. Rapid UF rate during the HD session is apt to elicit an inadequate intravascular refilling [29]. Therefore, an optimal setting in UF rate during the HD session should be anticipated to avoid the occurrence of IDH during the HD session. The full-adjusted model analyses revealed a positive correlation between the BMI levels and IDH during the HD sessions. However, the individual effects of leading factors disappeared during the multi-factor interaction analyses. To delineate BMI association with IDH, we suggest a large dataset analyses in the future.

This study considered 25 factors from the clinical data, which included the medical records and laboratory measurements. All the factors were tested and their multi-factor interaction were analyzed simultaneously using the DNN model. To our knowledge, the prediction of the occurrence of IDH as the outcome of the HD treatments has not been previously used as a tuning factor in the computational models. The best model to analyze the multi-factor interaction was trained and validated by using the cross-validation approach. The multifactor interaction model achieved better accuracies than all-factor association model in IDH occurrence. The 4-factor interaction model reported the highest performance in predicting the occurrence of IDH during HD. The 4-factor to 6-factor interaction models included the hypertension, UF coefficient, UF rate, and UF amount as the factors for predicting IDH during HD, which is consistent with the full-adjusted multivariate regression analysis. Hence, the outcomes of the multi-factor interaction model may potentially contribute in the prediction of the occurrence of IDH during HD.

There are limitations of using the deep learning model in the present study. First, the included clinical variables could not cover the whole etiology of the occurrence of IDH during the HD sessions, such as, severe medical diseases that produce immediate hemodynamic changes when HD is initiated, medicine uptake history, real time awareness of the occurrence IDH by the nursing staff, and other subtle conditions not identified by the deep learning model. Second, the fundamental limitation arises from the nature of the deep networks, in which the neural network includes only the clinical variables proposed by the medical staff. It is possible that several unknown variables might have been missed, and therefore, not included in the algorithm used in the present study. Meanwhile, it is noteworthy that understanding what kind of deep neural network to be used for the prediction of a clinical condition is still not an area of active research. We present the first study using a deep learning scheme to predict the occurrence of IDH during the HD sessions. However, the accuracy rate could not achieve a satisfactory status. Hence, this algorithm cannot be used as a replacement to the comprehensive medical care during HD session. The validation of this algorithm requires further analyses involving a

larger dataset, which may need a consensus from the experts on more confounding factors.

V. CONCLUSION

The present study demonstrated that a deep learning scheme is a potential tool to determine the clinical factors associated with the occurrence of IDH during an HD session. The main goal of the future investigation may be to develop a satisfactory deep learning performance model based on the analyses of a larger dataset. To our knowledge, this is the first attempt of applying a DNN model including clinical variables to predict the occurrence of IDH during an HD session. In the future, we expect this model to achieve precision in predicting IDH by including more clinical samples and factors for analyses.

ACKNOWLEDGMENT

The protocol for the study was approved by the Committee of Human Research at Kaohsiung Chang Gung Memorial Hospital (IRB no: 201800595B0) for a retrospective review of the medical data.

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