



## Construction and Comparison of a Machine Learning Risk Model for Lower Extremity Deep Vein Thrombosis in Patients with Coronavirus Disease 2019

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### Abstract

**Objective:** To predict the risk of Deep Venous Thrombosis (DVT) in patients with Coronavirus Disease 2019 (COVID-19) after routine anticoagulation using logistic regression, Support Vector Machine (SVM) and neural network models.

**Methods:** The Hospital Information System was used to obtain patients' data based on the Virchow triad. The data were randomly divided into training (70%) and testing (30%) sets. Logistic regression, SVM models and neural networks were also considered. Based on the testing data, each model's performance was evaluated using confusion matrices for the prediction, sensitivity, area under the curve and F1 score.

**Results:** A dataset with 357 patients with COVID-19 was used, and 172 (48.4%) of them developed lower extremity DVT. A 15-variable model was examined. The area under the receiver operating characteristic curve of logistic regression, SVM and neural network was 0.844 (95% Confidence Interval [CI]: 0.773, 0.916), 0.781 (95% CI: 0.689, 0.872) and 0.879 (95% CI: 0.814, 0.945), respectively. DeLong's test showed no statistical significance in the ROC between different models.

**Conclusion:** Three prediction models were created using the Machine Learning (ML) algorithm, which could predict the DVT risk in COVID-19 patients. This study shows that ML may be crucial in estimating the risk of DVT in patients with COVID-19 and provides a reference for improving the accuracy of predicting the risk of DVT.

**Keywords:** Machine learning; Artificial intelligence; SVM model; Neural Network; DVT; COVID-19

### Introduction

Coronavirus Disease 2019 (COVID-19) is a type of bilateral interstitial pneumonia and acute respiratory distress syndrome caused by SARS-CoV-2 infection. It is an acute, complicated systemic condition with symptoms ranging from asymptomatic to severe with a high mortality risk [1,2]. The pathophysiology of the disease and subsequent coagulopathy produce an inflammatory, hypercoagulable and hypofibrinolytic state [3,4]. This makes COVID-19 patients the high-risk group for developing Deep Venous Thrombosis (DVT) of the lower limbs. Although current evidence indicates that routine anticoagulants are recommended to prevent thrombosis in hospitalized COVID-19 patients [5,6], the incidence of deep vein thrombosis in individuals with COVID-19 remains high. A meta-analysis involving 3,342 patients with COVID-19 showed that the DVT incidence in COVID-19 patients was about 14.8% (95% CI: 8.5, 24.5) [7]. The DVT incidence in critically ill COVID-19 patients can be as high as 46% (95% CI: 35%-56%) [8]. COVID-19 patients with DVT have poorer oxygenation index, higher rate of cardiac injury and worse prognosis, including a higher proportion of deaths and a lower proportion of discharged patients [9] compared to COVID-19 patients without DVT. Therefore, it is vital to accurately assess the thrombus incidence in COVID-19 patients and implement individualized thrombus prevention and nursing.

Machine Learning (ML), a subfield of artificial intelligence, allows for managing large and

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complex data sets, identifying patterns and making predictions. In recent years, ML has been gradually applied to biomedicine [10]. Machine learning techniques offer many advantages over conventional statistical models, including high power and accuracy, the capacity to model non-linear effects, the interpretation of sizeable genomic data sets, robustness to parameter assumptions and the elimination of the need for a normal distribution test. Currently, several studies have applied ML to predict the risk of Venous Thromboembolism (VTE) (including DVT and Pulmonary Embolism [PE]), while few studies have used it to DVT in patients with COVID-19 [11-13].

The mechanism of thrombosis is mainly the Virchow triad (coagulation dysfunction, vascular wall injury and slow blood flow). Based on the Virchow triad, a risk model for DVT in COVID-19 patients was built in this study. The model incorporated relevant blood indicators for these three aspects, including coagulation indicators, inflammatory indicators and NT-proBNP, which has a specific reference for thrombosis prevention.

In this study, we utilized ML algorithms to build three prediction models to assess the risk of DVT in COVID-19 patients and compare the predicted accuracy of the three models to determine the most accurate model.

## Material and Methods

### Study design and participants

Based on previous studies, we identified relevant variables and [14-17] developed and validated the models.

In the final dataset, we considered 15 variables and divided them into five separate categories: (1) patient characteristics, including age and body mass index, (2) indicators of coagulation, including prothrombin time, international normalized ratio, fibrinogen, activated partial thromboplastin time and thrombin time, (3) Hemodynamic measures, including NT-proBNP, (4) markers of inflammation including C-reactive protein, IL6, TFN- $\alpha$ , IFN- $\gamma$ , neutrophil-to-lymphocyte ratio and (5) COVID-19-related factors, including the length of stay and classification of COVID-19.

Patient data from the First Affiliated Hospital of Wenzhou Medical University were retrospectively collected between December 2022 and February 2023 using the Hospital Information System (HIS). The data collection included the above 15 variables. Patients' inclusion criteria: (1) Age  $\geq$  18 years old; (2) All patients met the diagnostic criteria according to the World Health Organization interim guidance and received hospital treatment; (3) patients received routine anticoagulant prophylaxis during hospitalization. Patients' exclusion criteria; (1) patients with superficial vein thrombosis; (2) patients with DVT of the lower extremity before admission; (3) there are contraindications related to physical and drug therapy; (4) patients with severe coagulation dysfunction and (5) the required clinical data is incomplete.

In this study, anticoagulants were administered depending on the patient's weight and disease progression. Consumption of one type of anticoagulant does not rule out the possibility of the patient consuming another type of anticoagulant. We collected patients' use of anticoagulants and divided them into the following categories: Enoxaparin, nadroparin calcium, low-molecular-weight-heparin, Unfractionated Heparin (UFH) and rivaroxaban. A literature review revealed no significant variations in the occurrence of venous thromboembolism events across different types of anticoagulants [5,18,19].

### Classification of COVID-19

The classification of COVID-19 was divided into mild, moderate and severe types [20-22]. Mild type: No radiographic signs of pneumonia exist, and the clinical symptoms are mild. Moderate type: Patients experience fever and respiratory tract symptoms, and imaging can reveal pneumonia signs. Severe type: Adults who meet any of the following criteria: Respiratory rate 30 breaths/min; oxygen saturation  $\leq$  93% at a rest state; arterial partial Pressure of Oxygen (PaO<sub>2</sub>)/Oxygen Concentration (FiO<sub>2</sub>)  $\leq$  300 mmHg, patients with >50% lesions progression within 48 h in lung imaging.

### Diagnosis of DVT

In this study, superficial vein thrombi (such as those in the soleus vein or gastrocnemius vein) were excluded due to the limited clinical relevance of superficial veins (great saphenous veins or small saphenous veins) or myenteric veins. Experienced sonographers have examined the blood vessels in the lower limbs using color Doppler ultrasound to check for DVT. The following were primarily included in the color Doppler ultrasonography diagnostic criteria for DVT: 1. Unusual echoes. 2. The vein beneath the ultrasound probe at the damaged spot should not be compressed shut. 3. The venous thrombus segment showed no clear indication of blood flow. 4. A reduction in the affected limb's blood flow and vascular width. Using postoperative vascular color Doppler ultrasonography, the patients were separated into two groups: Patients with DVT (thrombus group; 174 cases) and patients without DVT (non-thrombus group; 183 cases).

### Statistical analysis

A database of admission information and blood samples from the two groups was established using Excel 2016; statistical analysis was carried out using SPSS 26. The normal distribution and homoscedasticity were assessed using the Shapiro-Wilk and Levene tests, respectively. Measurements conforming to a normal distribution were expressed as the mean  $\pm$  standard deviation (mean  $\pm$  SD). Moreover, the measurement data were expressed as the median [P50 (P25, P75)], and the classified data were expressed as a case (percentage) [N (%)]. The chi-square, t-test and Mann-Whitney U tests were used to compare the basic admission data.

The dependent variable  $y$  is a dichotomous variable with the values 1 and 0 defining the occurrence and absence of DVT, respectively. This is a binary sorting task because the ML algorithm learns rules to distinguish between two outcome categories: the occurrence and non-occurrence of DVTS.

The samples were randomly divided into a training set (70%) for model development and a test set (30%) for model validation (Figure 1). All 15 variables were included in the model, and the features were standardized using the Mapminmax function in Matlab to achieve feature scaling. R Studio was used to perform a correlation analysis of the attributes. The optimal parameters of the Support Vector Machine (SVM) model were then determined using 10-fold cross-validation. The logistic regression, neural network and SVM were implemented using SPSS 26.0 and Matlab R2016b, respectively. DeLong's test is conducted using R Studio.

Data in the testing set were measured to assess the predictive capabilities of the three models. The predictive capabilities of the three models were compared using the six evaluation matrices, including accuracy, precision, recall, specificity, F1-score and the Area under the Receiver Operating Characteristic Curve (AUROC)

**Table 1:** Comparison of general data of COVID-19 patients between DVT group and non-DVT group.

Variables	Total (357)		DVT (174)		Non-DVT (183)		$\chi^2/t/Z$	P
	Mean $\pm$ SD/ $P_{50}$ ( $P_{25}$ , $P_{75}$ )	n (%)	Mean $\pm$ SD/ $P_{50}$ ( $P_{25}$ , $P_{75}$ )	n (%)	Mean $\pm$ SD/ $P_{50}$ ( $P_{25}$ , $P_{75}$ )	n (%)		
Gender							0.017	0.895
Male		251 (70.3)		134 (77.0)		142 (77.6)		
Female		106 (39.7)		40 (23.0)		41 (22.4)		
Age (years)	74.55 $\pm$ 11.73		77.32 $\pm$ 9.16		71.91 $\pm$ 13.24		-4.511	<0.001
Classification of COVID-19 n(%)							-1.779	0.075
1 (Mild type)		7 (2.0)		0 (0)		7 (3.8)		
2 (Moderate type)		147 (41.2)		68 (39.1)		79 (43.2)		
3 (Severe type)		203 (56.8)		106 (60.9)		97 (53.0)		
LOS (days)	19 (10,25)		22 (15,30)		14 (8,23)		-6.186	<0.001
BMI (kg/m <sup>2</sup> )	23.51 (21.37,25.01)		23.70 (21.61,25.25)		22.66 (21.26,24.84)		-1.685	0.092
PT (s)	14.3 (13.6,15.5)		14.60 (13.80,15.93)		14.20 (13.40,15.20)		-2.904	0.004
INR	1.11 (1.04,1.23)		1.13 (1.06,1.27)		1.09 (1.01,1.19)		-3.094	0.002
FIB (g/L)	4.30 $\pm$ 2.05		3.83 $\pm$ 1.99		2.01 $\pm$ 4.74		-4.13	<0.001
APTT (s)	36.4 (33.1,41.6)		35.70 (32.75,43.50)		36.70 (33.40,40.30)		-0.249	0.803
TT (s)	18.6 (17.2,18.6)		18.80 (17.30,21.00)		18.40 (17.10,20.20)		-1.611	0.107
NT-proBNP (ng/L)	967 (380,2612.5)		987 (450,3012.5)		914 (309,1992)		-1.882	0.06
CRP (mg/L)	40.40 (11.65,98.20)		34.85 (10.00,91.00)		45.20 (12.80,101.40)		-1.453	0.146
IL6 (pg/mL)	37.36 (4.69,223.02)		51.97 (15.62,423.86)		24.18 (1.41,95.41)		-4.623	<0.001
TFN (pg/mL)	0.10 (0.10,0.28)		0.10 (0.10,0.24)		0.10 (0.10,0.28)		-0.192	0.847
IFN (pg/mL)	0.10 (0.10,1.68)		0.10 (0.10,2.32)		0.10 (0.10,1.24)		-1.185	0.236
NLR (%)	17.81 (8.67,29.50)		19.00 (11.78,30.66)		16.30 (7.11,17.7)		-2.166	0.03

LOS: Length of Stay; BMI: Body Mass Index; PT: Prothrombin Time; INR: International Normalized Ratio; FIB: Fibrinogen; APTT: Activated Partial Thromboplastin Time; TT: Thrombin Time; CRP: C-Reactive Protein; NLR: Neutrophil-to-Lymphocyte Ratio

to select the optimal model. The formula for calculating each index is as follows: Accuracy = (True positive + True negative)/(True positive + False negative + True negative + False positive). Precision = True positive/(True positive + False positive). Recall = True positive/(True positive + False negative). Specificity = True negative/(True negative + False positive). F1 = (2  $\times$  precision  $\times$  recall)/(precision + recall). The AUROC is a graphical plot showing the diagnostic capability of a binary classifier as its discrimination threshold changes. The closer the AUROC results are to 1, the better the model performance [23].

## Results

### General characteristics

We included 357 COVID-19 patients (74.55  $\pm$  11.73 years; 251 (70.3%) male). The patients' general baseline characteristics are described in detail in Table 1. Patients were divided into two groups based on the findings of the vascular color Doppler ultrasonography: those with DVT (DVT group; 174 cases) and those without DVT (non-DVT group; 183 cases). Patient characteristics are shown in Table 1.

### Feature correlation analysis

Correlation analysis showed that nine characteristic variables had statistical significance for the occurrence of DVT in COVID-19 patients, including age, COVID-19 classification, length of stay, PT, INR, FIB, TT, NT-proBNP and IL-6. The three characteristics with the strongest correlations were the length of stay, age and FIB (Figure 2).

### Performance and validation of the models

The performance results of the training and the testing groups

of the three models are shown in Tables 2 and 3, respectively. The accuracy (77.78%), precision (77.59%), specificity (75.00%), F1 score (0.79) and AUROC (0.879) of the neural network were better than those of the other two models. As for recall (81.82%), logistic regression was higher than the neural network and SVM.

In order to make the prediction results of the model clearer, we construct the confusion matrix (Figure 3, 4). The main diagonal number of the confusion matrix represents the model's accurate prediction. The ratio of the sum of the diagonal elements to the sum of all the elements of the confusion matrix is called 'Precision'.

Figure 3 shows that logistic regression was able to answer correctly 'DVT' 45 times and 'Non-DVT' 35 times, while it made an error 10 times by answering 'Non-DVT' when the correct answer was 'DVT' (Figure 3).

The SVM was able to answer correctly 'DVT' 45 times and 'Non-DVT' 37 times, while it made an error 11 times by answering 'Non-DVT' when the correct answer was 'DVT' (Figure 4). The confusion matrix of the neural network is shown in Figure 5.

Figure 6 shows the AUROC of different models. DeLong's test [24] was used to compare the AUC of different models, and the results showed that there was no statistical difference in the predictive value of different models ( $P > 0.05$ ) (Table 4).

## Discussion

ML is vital in interpreting complex medical data. Artificial intelligence is increasingly employed successfully in the medical field [25-27]. In this study, ML models were employed to evaluate the risk of DVT in hospitalized COVID-19 patients.

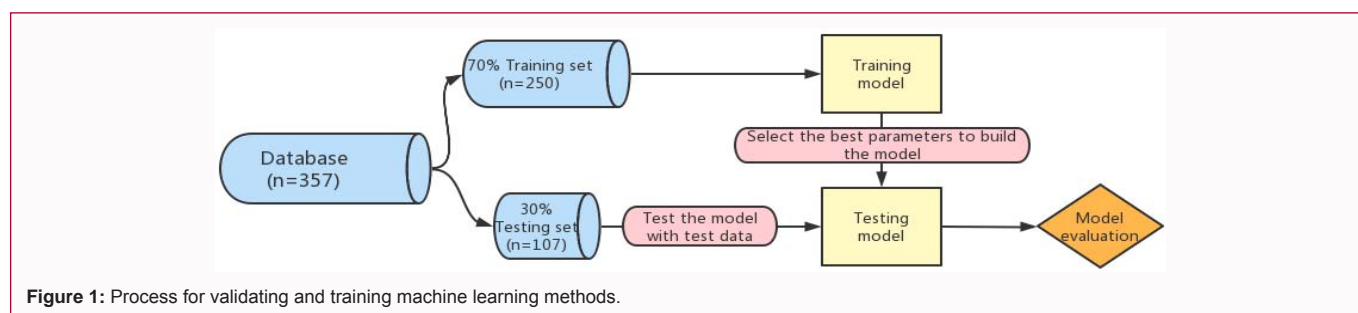
**Table 2:** Performance results of three models in the training set.

Method	Acc (%)	Pre (%)	Rec (%)	Spe (%)	F1	AUROC (95%CI)
Logistic regression	69.88	68.7	66.95	72.52	0.68	0.784 (0.728,0.841)
SVM	100	100	100	100	1	1
Neural Network	78.54	78.76	75.42	81.4	0.77	0.857 (0.812,0.902)

**Table 3:** Performance results of three models in the testing set.

Method	Acc (%)	Pre (%)	Rec (%)	Spe (%)	F1	AUROC (95% CI)
Logistic regression	74.77	72.58	81.82	67.31	0.77	0.844 (0.773,0.916)
SVM	76.63	76.27	80.36	72.55	0.78	0.781 (0.689,0.872)
Neural Network	77.78	77.59	80.36	75	0.79	0.879 (0.814,0.945)

Acc: Accuracy; Pre: Precision; Rec: Recall; Spe: Specificity; F1: F1-score; SVM: Support Vector Machine



**Figure 1:** Process for validating and training machine learning methods.

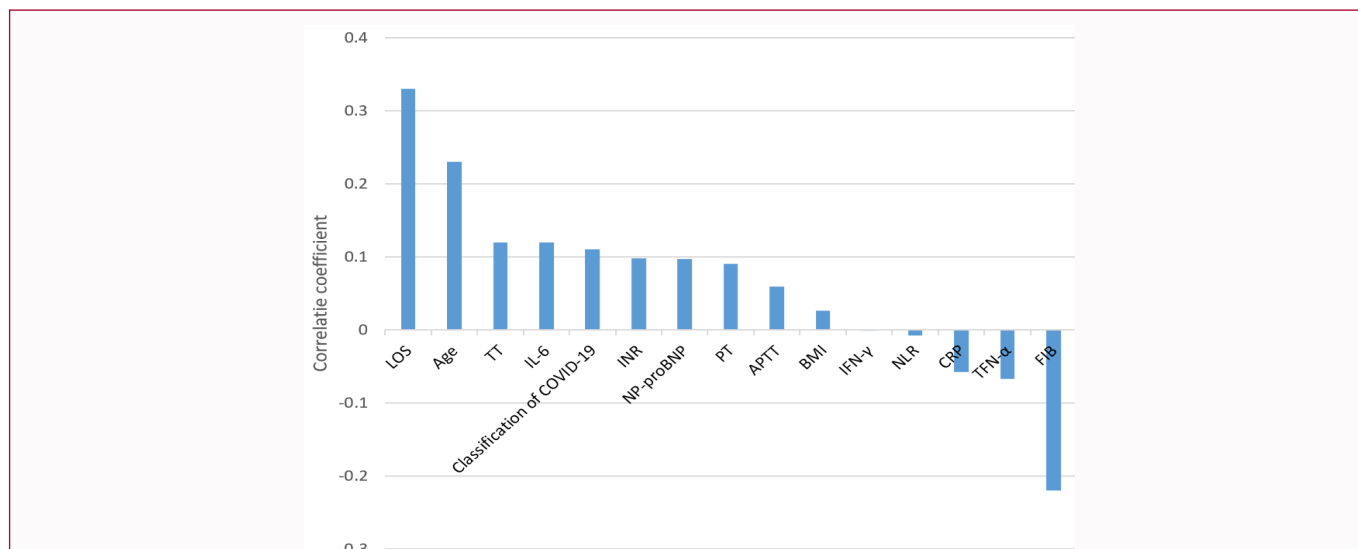
**Table 4:** Comparison of ROC between three models.

Model combination	Z	P
LG x SVM	1.0721	0.285
LG x NN	-0.8864	0.375
SVM x NN	-1.7244	0.086

The results provide some risk predictors for DVT in hospitalized patients with COVID-19. The influence of the Length of Stay (LOS) and age on the development of venous thromboembolism is widely acknowledged as the two most strongly correlated indicators [28,29].

Because of the prolonged hospitalization, the patient’s range of motion is significantly reduced, resulting in blood stasis, which increases the likelihood of DVT. Risk factors such as poor venous valve function and blood disruption in elderly patients will also increase the risk of DVT.

Blood indices corresponding to the three elements of the Virchow triad also had statistical relevance for DVT formation in COVID-19 patients. Among these, FIB was negatively correlated with the occurrence of DVT in COVID-19 patients, which is consistent with the results of previous studies [14]. These findings might be explained



**Figure 2:** Correlation of all features with DVT.

LOS: Length of Stay; BMI: Body Mass Index; PT: Prothrombin Time; INR: International Normalised Ratio; FIB: Fibrinogen; APTT: Activated Partial Thromboplastin Time; TT: Thrombin Time; CRP: C-Reactive Protein; NLR: Neutrophil-to-Lymphocyte Ratio

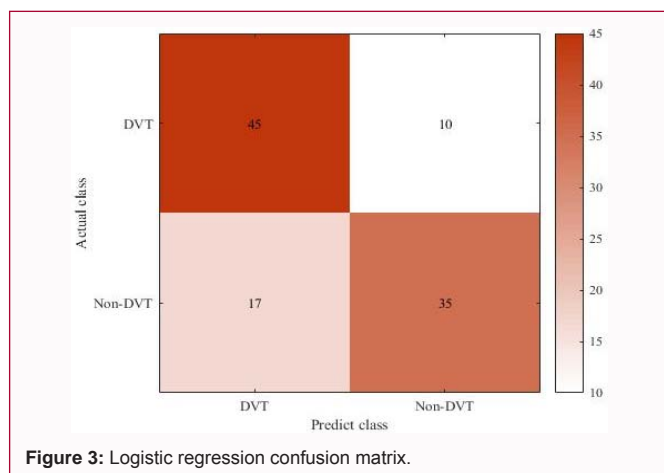


Figure 3: Logistic regression confusion matrix.

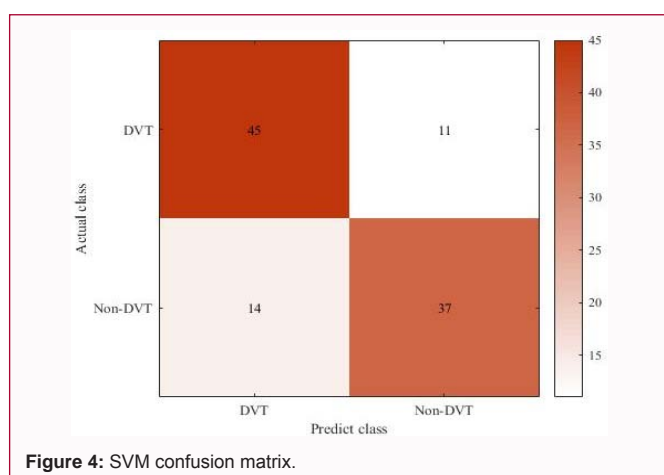


Figure 4: SVM confusion matrix.

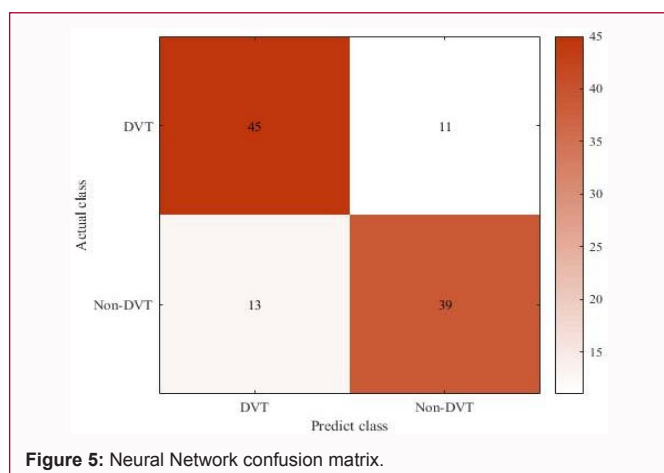


Figure 5: Neural Network confusion matrix.

by the idea that patients with pulmonary thromboembolism might ingest more fibrinogen during the thrombosis process [30].

The study discovered that NT-proBNP levels were related to the risk of VTE in patients [16,31]. AR Folsom et al. found a strong positive correlation between NT-proBNP and the incidence of VTE among 9,844 subjects after a median of 17.6 years (max 19.9) [32]. Therefore, this study uses NT-proBNP as a hemodynamic indicator to investigate the relationship between NT-proBNP and DVT. The results demonstrated that NT-proBNP in COVID-19 patients was significantly higher than the normal level (0–125 ng/L), and NT

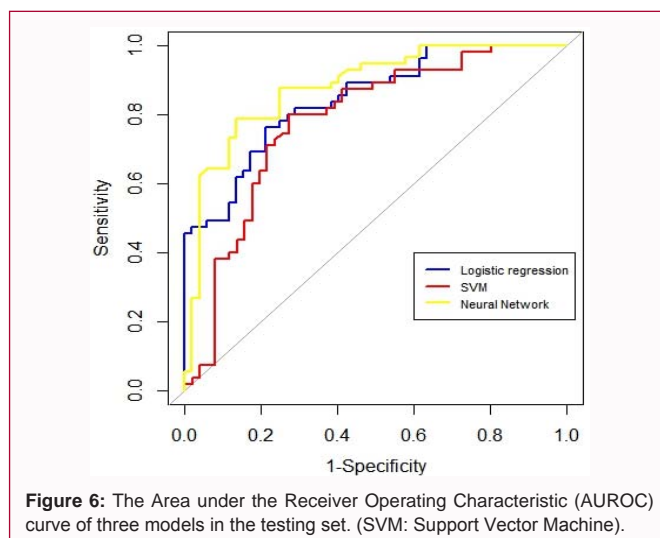


Figure 6: The Area under the Receiver Operating Characteristic (AUROC) curve of three models in the testing set. (SVM: Support Vector Machine).

level was positively correlated with the risk of DVT. Thus, one of the prognostic indicators of COVID-19 patients may be the level of NT-proBNP.

Cytokines, including IL-6, are closely associated with thrombosis [33]. Our study also showed that IL-6 levels in the DVT group were significantly higher than those in the non-DVT group. In addition, IL-6 levels in COVID-19 patients in this study ( $450.55 \pm 1448.82$  pg/mL) were significantly higher than the normal value ( $<3$  pg/mL), which were the same as the results of previous studies [34]. However, the causal relationship between IL-6 and venous thrombosis is still being debated and further human studies are required to verify it.

The logistic regression SVM and neural network models developed in this study have accuracy rates of 74.77%, 76.63% and 77.78%, respectively, and were successful in accurately predicting the occurrence of DVT in COVID-19 patients. The AUROC of the three models was 0.844 (95% CI: 0.773, 0.916), 0.781 (95% CI: 0.689, 0.872) and 0.879 (95% CI: 0.814, 0.945), respectively. All three models performed similarly in DeLong's test and accurately predicted the risk of deep vein thrombosis in COVID-19 patients. Considering the clinical significance of variables and the limitation of sample size, we incorporated all 15 variables into the models. Although the model has many variables, they could be captured from the hospital HIS system. In the future, we can integrate the model into an HIS system to improve efficiency and make patient DVT evaluation more convenient.

## Limitations of the Study

First, due to this study's retrospective nature, the model's significance has not been evaluated in a prospective cohort. Second, only two common ML models were included in our study; additional models may be added to allow for comparison. Furthermore, because patients vary, the varieties of traditional anticoagulants have not been unified, allowing categorized investigations to be carried out in the future.

## Conclusion

In this study, using the ML method, three predictive models were used to assess the risk of DVT in hospitalized COVID-19 patients. All three models can effectively predict the risk of DVT in COVID-19 patients. The study suggests that ML could be essential in DVT risk

assessment in COVID-19 patients. We hope to integrate additional clinically relevant models and larger data sets to improve the results in the future.

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Y.C. conceived the idea and designed the study. L.Z., R.Y., K.C. and Y.Z. collected the relevant data. L.Z. and Y.Z. prepared the figures and tables. L.Z., R.Y. and Y.Z. performed the statistical analyses. All the authors interpreted the data and contributed to preparation of the manuscript. L.Z. and R.Y. wrote the manuscript. All authors read and approved the final manuscript.

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