Pulmonary Embolism Risk Assessment in Acute Isolated Distal Deep Venous Thrombosis

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ABSTRACT

The clinical risk factors and risk of developing pulmonary embolism (PE) in patients with acute isolated distal deep venous thrombosis (IDDVT) were assessed using single complete-duplex ultrasound (CDUS) imaging to reduce over-testing and over-treatment. This observational study was conducted from January 2020 to December 2022. Retrospective analysis was performed on CT pulmonary angiography (CTPA), blood coagulation markers, myocardial injury markers, blood gas analysis, and CDUS imaging of the lower extremity blood vessels of 146 patients with newly diagnosed IDDVT. Binary logistic regression was used to evaluate the relationship between these indicators and PE. After stepwise regression analysis, the predictors included in the regression model were D-dimer (DD), the sum of the thrombus length, and the maximum value of the thrombus width, with odds ratios (ORs) of 1.307 ($p < 0.001$), 1.018 ($p = 0.005$), and 1.613 ($p = 0.018$), respectively. The combined prediction model achieved an area under the receiver operating characteristic curve (AUC) of 0.832 [95% confidence interval (CI): 0.761, 0.902]. By balancing the sensitivity and specificity of DD, combined single CDUS improves the predictive value for PE in patients with IDDVT.

Key Words: *Venous thrombosis, Pulmonary embolism, Ultrasonography, D-dimer, Diagnosis.*

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Similar to acute proximal deep vein thrombosis (DVT), the severe complication of isolated deep venous thrombosis (IDDVT) is the possibility of PE, which has a high mortality rate and seriously threatens patients' lives.[1] CT pulmonary angiography (CTPA) is the preferred method for diagnosing PE, as it can intuitively show the location of pulmonary artery thrombosis and the degree of vascular blockage.[2] However, CTPA has disadvantages such as radiation exposure, contrast reactions, high-cost, and time consumption to complete.[3] Avoiding unnecessary radiation exposure and achieving early diagnosis of PE in IDDVT patients are important, but there is still no unified standard for determining when CTPA is necessary for acute IDDVT. The purpose of this study was to identify potential or related clinical factors of PE in IDDVT patients and evaluate the value of single ultrasound imaging instead of serial imaging, ultimately helping clinicians determine the need for further CTPA.

This observational study was conducted at the Affiliated Hospital of Yunnan University, China, from January 2020 to December 2022.

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The study was carried out after obtaining approval from the Hospital's Ethical Committee. Only patients who had undergone CTPA, had available coagulation marker results, and had good imaging quality on the retained ultrasound images within 7 days after symptom onset or admission were included. Patients who had recently received thrombolytic or anticoagulant therapy were excluded.

Ultrasonic examination consisted of a complete duplex ultrasound (CDUS) protocol, from the thigh to the ankle, employing compression and colour doppler at selected sites, according to the Consensus Conference of the Society of Radiologists in Ultrasound.[4] Patients with high-quality ultrasound image retention were screened for inclusion in the retrospective analysis of the internal diameter, display length, recorded maximum width, width sum, maximum length, length sum, number of thrombi, and whether the thrombi were unilateral or bilateral. Subsequently CTPA was performed with an iodine contrast agent (Iopamidol 370 mg I/mL). Patients were scanned from the thoracic inlet to the diaphragmatic level. The region of interest (ROI) was placed in the main pulmonary artery, and the triggering threshold was set at 200 HU. After 5.5 seconds of drug injection, the patient was instructed to hold their breath in a state of natural respiration. When the threshold was reached, the scanning started (from cephalic to foot), and the images were transmitted to the picture archiving and communication system (PACS) after scanning.

Table I: The comparison of ultrasonic indicators and laboratory indices between the control group and the PE group.

	Control Group	PE Group	p-value
Ultrasonic indicators	**n = 83**	**n = 63**	
Sum of lengths, mean ± SD (mm)	58.74 ± 26.8	95.65 ± 46.22	<0.001*
Maximum length, mean ± SD (mm)	40.76 ± 12.11	55.12 ± 17.29	<0.001 *
Sum of widths, mean ± SD (mm)	7.81 ± 3.53	11.67 ± 5.7	<0.001*
Maximum width, mean ± SD (mm)	5.3 ± 1.45	6.86 ± 1.97	<0.001*
Unilateral or bilateral (N)	83	63	0.507
Unilateral N (%)	59 (71.1%)	44 (69.8%)	>0.05
Bilateral N (%)	24 (28.9%)	19 (30.2%)	>0.05
Laboratory index	**Mean ± SD**	**Mean ± SD**	
Erythrocyte count, mean ± SD, 10^12/L	4.14 ± 0.74	4.06 ± 0.69	0.478
Haemoglobin, mean ± SD, g/L	125.99 ± 23.61	124.01 ± 24.71	0.622
Haematocrit, mean ± SD, %	0.38 ± 0.07	0.37 ± 0.07	0.501
Prothrombin time, mean ± SD, s	12.01 ± 1.38	11.76 ± 1.20	0.253
Antithrombin III, mean ± SD, %	83.13 ± 19.99	87.27 ± 20.00	0.217
D-dimer, median (Q1-Q3), ug/ml	3.3 (1.7 - 4.7)	4.9 (2.4 - 7.4)	<0.001*
Platelet count, median (Q1-Q3), 10^9/L	260 (190 - 312)	231 (182 - 280)	0.263
Thrombocytocrit, median (Q1-Q3), %	0.25 (0.2 - 0.32)	0.24 (0.19 - 0.29)	0.251
Mean platelet volume, median (Q1-Q3), fL	10 (9.4 - 10.6)	9.9 (9.4 - 10.8)	0.857
Platelet distribution width, median (Q1-Q3), %	11.4 (10.2 - 12.7)	10.9 (10.0 - 13.0)	0.536
Macroplatelet ratio, median (Q1-Q3), %	25.3 (19.8 - 30.3)	22.9 (19.7 - 31.4)	0.770
Ratio of international normalisation median (Q1-Q3)	1.0 (0.92 - 1.11)	0.98 (0.93 - 1.08)	0.585
Fibrinogen, median (Q1-Q3), g/L	3.6 (2.53 - 4.6)	3.8 (2.9 - 5.2)	0.104
Thrombin time, median (Q1-Q3), s	17.1 (16.2 - 18.4)	17 (15.7 - 18)	0.432
Activated partial thrombin time, median (Q1-Q3), s	27.1 (24.6 - 29.6)	26.4 (24.6 - 28.2)	0.315
Fibrinogen degradation products, median (Q1-Q3), ug/ml	7.3 (3.4 - 11.5)	11.1 (4.5 - 15.8)	0.020*

Categorical variables were compared using the χ^2 test, continuous variables were compared using the independent samples t-test for normal distribution, and the Mann-Whitney U test for non-normal distribution. p <0.05 indicates the difference between the PE group and the control group was statistically significant. PE = Pulmonary embolism.

Categorical variables were summarised as frequencies and percentages. Continuous variables were summarised as the mean ± SD or median (Q1-Q3), depending on the distribution of the data. Categorical variables were compared using the χ^2 test, while continuous variables were compared using the independent samples t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables (determined by the Shapiro-Wilk's test). The analysis was conducted using SPSS version 23. Each risk factor was examined separately through binary logistic regression analysis, using univariable and multivariable analyses. The validity of the mathematical model was evaluated through receiver operating characteristic curve (ROC curve) analysis, and the area under the ROC curve (AUC) was measured. A p-value <0.05 was considered statistically significant.

A total of 146 patients with IDDVT included 71 (48.6%) males and 75 (51.4%) females. Based on the CTPA results, the patients were divided into two groups: The PE group and the control group (non-PE group). The results of the difference analysis revealed that statistically significant differences (p <0.05) existed between the two groups in terms of sum and maximum length of thrombus, sum and maximum width of thrombus, D-dimer levels, and fibrinogen degradation products, as shown in Table I.

After stepwise regression analysis, the predictive factors included in the regression model were DD, the sum of the thrombus length, and the maximum thrombus width, with odds ratios (ORs) of 1.307 (p = <0.001), 1.018 (p = 0.005), and 1.613 (p = 0.018), respectively. The model was significant; it correctly classified 79.5% of the cases. The Hosmer–Lemeshow test showed a p >0.05. Based on the results, the regression equation was retained according to the following formula: logit (p) = -5.672 + 0.017*X1 + 0.478*X2 + 0.268*X3 (X1 = the sum of the thrombus length, X2 = the maximum thrombus width, X3 = DD).

The combined prediction model using length-width-DD had a diagnostic sensitivity of 76.2% and a specificity of 84.3%. The AUC was significantly increased to 0.832 (95% CI: 0.761-0.902; p <0.001) compared to using a single index alone (p <0.05), as shown in Figure 1.

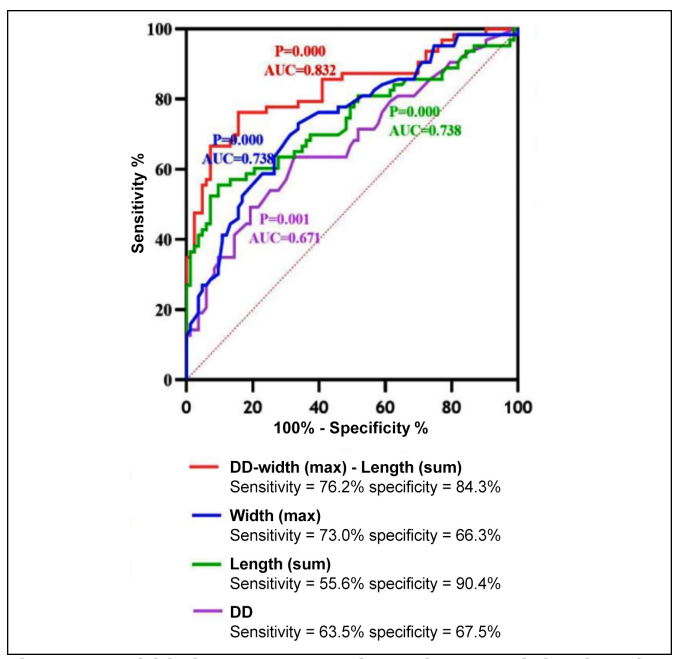

Figure 1: Multi-index ROC curve of DD, the sum of the thrombus length, the maximum thrombus width, and the regression model for PE diagnosis. DD = D-dimer, Width (max) = the maximum thrombus width, length (sum) = the sum of the thrombus length.

The management of IDDVT is controversial,[1] with no clear consensus across guidelines on whether IDDVT needs CTPA to exclude PE and / or should be treated with antico-agulants.[5] According to the existing diagnostic guidelines, serial ultrasound imaging of calf veins for two weeks is suggested over anticoagulation therapy (Grade 2C) in patients.[6] However, this choice could potentially encourage unnecessary tests and procedures, exposing patients to the risk of overtreatment and prolonging their hospital stay. Therefore, this study primarily focused on a retrospective analysis of patients with acute IDDVT within 7 days. Compared to serial imaging, this study highlights the importance of a single CDUS imaging, including the maximum thrombus width and the sum of the thrombus length, in predicting the occurrence of PE in the patients. The authors found that quantitative diagnoses of vein thrombosis (including the maximum width, the sum of the width, the maximum length, and the sum of the length) are crucial for diagnosing PE. When the sum of the thrombus length reached 92.75 mm and the maximum thrombus width reached 5.65 mm, the ultrasound indicators in IDDVT patients showed a high predictive value for PE. Thus, the maximum thrombus width and the sum of the thrombus length were selected as significant variables during the establishment of a regression model with high diagnostic value.

The median DD level was 3300 ng/mL in patients without pulmonary infarction, while the median DD level was higher in the PE group (4900 ng/mL). In the individual analysis of DD, the Youden index was highest when the DD level reached 4150 ng/mL, with a sensitivity of 63.5% and a specificity of 67.5%. Therefore, significantly elevated DD levels increase the likelihood of PE but decrease the diagnostic value and sensitivity. A regression model was obtained after combining ultrasound diagnosis which balanced the sensitivity and specificity of each diagnostic index and improved the predictive value of a single index for PE. This study demonstrated that DD, the sum of the thrombus length, and the maximum thrombus width could independently or collectively predict the occurrence of PE in IDDVT patients. The prediction model, combined with the maximum DD, thrombus length, and thrombus width values, significantly improved the prediction of PE in IDDVT patients. Due to the limitation of the sample size, few variables were eventually included in the regression equation, and the inclusion criteria were strict ($p < 0.05$), which may have filtered out some variables with diagnostic values that had a p-value <0.1. Other investigations, preferably prospective studies, are needed to expand the sample size to verify these findings.

The significance of this study is to assist clinicians in deciding whether to perform CTPA after detecting IDDVT, in order to exclude the possibility of PE. This can minimise unnecessary radiation exposure for low-risk patients, reduce over testing, and prevent unnecessary prolongation of hospital stays.

ETHICAL APPROVAL:
The Ethics Review Committee of the Affiliated Hospital of Yunnan University, The Second People's Hospital of Yunnan Province, Kunming, China, approved this study (Decision Number: 2022015, Dated: 23 February 2022).

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COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
JZ: Material and data collection and processing, drafting of the manuscript, and revising for important intellectual content.
JW: Interpretation and data analysis of the manuscript.
YL: Study design and comprehensive revision of the work.
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