The Diagnostic Efficacy of Age-Adjusted D-Dimer Cutoff Value and Pretest Probability Scores for Deep Venous Thrombosis

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Abstract

This study seeks to evaluate the diagnostic value of D-Dimer Plus and Innovance D-Dimer as well as the age-adjusted cutoff value for D-dimer detection in combination with 4 pretest probability (PTP) scores for deep venous thrombosis (DVT). A total of 688 patients referred for lower extremity vascular compression venous ultrasonography for suspected DVT from January 2016 to May 2018 in the First Affiliated Hospital of Sun Yat-sen University underwent D-dimer tests combining with 4 PTP scores. The diagnostic efficacy of the Wells score was the highest of the 4 PTP scores. The diagnostic efficacy of Innovance D-Dimer for DVT was greater than that of D-Dimer Plus, with better sensitivity and negative predictive value, which were both greater than 98%. If the cutoff values were adjusted by age, the Innovation D-Dimer could further improve both the specificity and the positive predictive value, providing better diagnostic performance. When the 2 D-dimer detections were used in combination with 4 PTP scores for DVT diagnosis, separately, both the positive predictive value and the negative predictive value significantly improved for D-Dimer Plus, and the positive predictive values significantly improved for Innovance D-Dimer. However, the sensitivity, specificity, and negative predictive values did not obviously change. For our patients, Wells score had the best diagnostic efficacy for our patients with suspected DVT among the 4 PTP scores. Innovance D-Dimer in combination with age-adjusted cutoff values exhibited increased sensitivity and negative predictive value for DVT diagnosis and was equivalent to the diagnostic efficacy of the Innovance D-Dimer in combination with PTP scores.

Keywords

age-adjusted cutoff value, D-dimer, deep venous thrombosis, diagnostic efficacy, pretest probability score

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Introduction

Given that the occurrence of deep venous thrombosis (DVT) is mostly concealed, the mortality is relatively high.[1,2] Consequently, if early diagnosis and thrombolytic therapy can be promptly achieved, the fatality rate of DVT will be greatly reduced. However, the definite diagnosis of DVT is generally based on imaging examinations, which are expensive, time-consuming, and partially invasive. These examinations may cause phlebitis and allergic reaction or aggravate DVT. Moreover, the clinical manifestations of DVT are mostly nonspecific, which results in unnecessary imaging examinations for a large number of non-DVT patients in clinical practice, greatly reducing the diagnostic efficacy.[3,4]

Combining the clinical pretest probability (PTP) scores with D-dimer values, current diagnostic guidelines for DVT demonstrated that patients with a high probability or plasma D-dimer concentrations greater than the critical value are classified as patients with suspected DVT, and these patients are subsequently further confirmed by imaging examinations, such as vascular ultrasound and angiography.[5] Internationally recognized PTP scores for DVT include Wells score,[5-7] St Andre score,[8] Kahn score,[9] and Constans score.[10] Each type of PTP score is designed for different races, dietary habits, disease

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Table 1. Four PTP Scores for DVT.

Wells Score		St Andre Score		Kahn Score		Constans Score	
Malignant tumor	+1	Malignant tumor	+1	Male	+1	Male	+1
Lower extremity paralysis or immobilization	+1	Lower extremity paralysis or immobilization	+1	Orthopedic operation within 6 months	+1	Lower extremity paralysis or immobilization	+1
Bedridden recently for ≥ 3 days	+1	Local warmth	+1	Local warmth	+1	Bedridden recently for ≥ 3 days	+1
Localized tenderness	+1	Unilateral pitting edema	+1	Superficial varicose veins	+1	Lower extremity enlargement	+1
Entire leg swollen	+1	Superficial varicose veins	+1			Unilateral leg pain	+1
Calf enlargement > 3cm	+1	Other reasonable diagnoses	−1			Other reasonable diagnoses	−1
Unilateral pitting edema	+1						
Superficial varicose veins	+1						
Previously documented DVT	+1						
Other reasonable diagnoses	−2					.	

Abbreviations: DVT, deep venous thrombosis; PYP, pretest probability.

spectra, and conditions. Therefore, certain differences in the clinical efficacy of PTP scores exist. Although the Wells score was widely used, the application of the other 3 PTP scores was rarely reported among Chinese populations. It is necessary to verify their clinical efficacies in this domestic patient population. A large number of studies have demonstrated that D-dimer detection can accurately exclude DVT in a short period of time and reduce patients' physical and economic losses.[11-16] Although the sensitivity and negative predictive value (NPV) of D-dimer in diagnosing DVT are relatively high, the specificity is relatively low, which limits its clinical application. There are numerous types of D-dimer reagents, and the sensitivity and the specificity of different reagents vary. According to the "2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism," age-adjusted cutoff values (age $\times$ 10 μg/L fibrin equivalent units [FEU], age > 50) were proposed for the improvement of specificity in D-dimer testing, which was used as a criterion for pulmonary embolism exclusion.[12] However, the application of this method has rarely been reported in Chinese populations. Hence, the purpose of this study was to compare the diagnostic efficacy of the 4 types of PTP scores, the 2 D-dimer reagents, and their combinations with age-adjusted cutoff values in patients with suspected DVT in our hospital.

Materials and Methods

Case Selection

A total of 688 patients referred for lower extremity vascular compression venous ultrasonography for suspected DVT from January 2016 to May 2018 in the First Affiliated Hospital of Sun Yat-sen University were enrolled in this study. Patients who did not complete either the clinical assessment or lower extremity vascular compression venous ultrasonography or patients who underwent simple anticoagulation or intravenous thrombolytic therapy were excluded. Patients who were under 18, pregnant, or puerperant were also excluded. The diagnosis of DVT was mainly based on compression venous ultrasonography. The inferior vena cava and the iliac, femoral, popliteal, and calf veins were examined by experienced angiologists. The diagnosis of all patients was confirmed in a 3-month follow-up period.

Four Types of PTP Scores

The items of the four PTP scores for DVT are listed in Table 1.

Methodology

D-dimer detection. Four milliliter of blood from each patient was collected into a tube containing sodium citrate anticoagulant (Becton Dickinson and Company, Franklin Lakes, New Jersey) prior to imaging examinations. Platelet-poor plasma was obtained by centrifugation at 3000 r/min for 10 minutes. The D-Dimer Plus kit and Innovance D-Dimer kit were used with Sysmex CA-7000 and Sysmex CS-5100 automatic coagulation analyzers, respectively. The detection process and reagent preparation were strictly in accordance with reagent instructions.

Pretest Probability Score. All the patients with suspected DVT were scored according to 4 PTP scores as mentioned above. The clinical scores of these patients were blindly scored by 2 doctors. The scores that were objectionable or questioned were rescored by a senior physician.

Age-adjusted cutoff value. Age $\times$ 10 μg/L FEU, age > 50.

Statistical Analysis

Data were processed using SPSS 19.0 statistical software. To evaluate the diagnostic value of the 4 PTP scores and the 3 plasma D-dimer assays for DVT, the sensitivity, specificity, positive predictive value (PPV), and NPV were calculated and compared using the χ^2 test. The receiver–operator characteristic curve (ROC curve) and the area under the curve (AUC) were used to compare their diagnostic efficacies for DVT. All data were presented as rate (%), and $P < .05$ was considered statistically significant.

Results

Clinical Characteristics

A total of 688 patients with suspected DVT from January 2016 to May 2018 in the First Affiliated Hospital of Sun Yat-sen

Table 2. Characteristics of Patients With or Without Deep Venous Thrombosis.

Characteristic	Thrombosis (n = 240)	No Thrombosis (n = 448)	P Value
Male sex	127 (52.92%)	291 (65.0%)	.002
Cancer	29 (12.08%)	73 (16.29%)	.139
Lower limb paralysis, immobilization	32 (13.33%)	16 (3.57%)	<.001
Confinement to bed >3 days	18 (7.50%)	18 (4.02%)	.051
Localized tenderness	52 (21.67%)	15 (3.35%)	<.001
Lower limb enlargement	29 (12.08%)	32 (7.14%)	.030
Calf enlargement >3 cm	199 (82.92%)	28 (6.25%)	<.001
Unilateral pitting edema	29 (12.08%)	16 (3.57%)	<.001
Superficial venous dilatation	10 (4.17%)	7 (1.56%)	.036
Previous deep venous thrombosis	5 (2.08%)	9 (2.01%)	.948
Local warmth	57 (23.75%)	33 (7.37%)	<.001
Unilateral lower limb pain	59 (24.58%)	15 (3.35%)	<.001
Orthopedic surgery >6 months	30 (12.50%)	32 (13.33%)	<.001

Table 3. The Scorings of 688 Patients With Suspected DVT in the 4 PTP Scores.

	Quantitative Indicators	Scorings	DVT (240)	Non-DVT (448)	Total
Wells score	9	≥2	114	40	154
		<2	126	408	534
St Andre score	6	≥2	28	12	40
		<2	212	436	648
Kahn score	4	≥2	52	11	63
		<2	188	437	625
Constans score	6	≥2	69	41	110
		<2	171	407	578

Abbreviations: DVT, deep venous thrombosis; PYP, pretest probability.

University were enrolled in this study. Of these patients (males 418, female 270, age range: 21-89 years, and mean age: 56.5 years), 240 were definitely diagnosed with DVT by lower limb vascular ultrasound, computed tomography, or venography (males 127 and females 113). The comparison of clinical characteristics between DVT and non-DVT is presented in Table 2.

Four Types of PTP Scores for Patients With Suspected DVT

According to the literature, all the 4 types of PTP scores presented above were classified into 2 groups: low possibility DVT group (score < 2) and high possibility DVT group (score ≥ 2). Score results are presented in Table 3.

Comparison of the Diagnostic Value of the 4 Types of PTP Score for DVT

The diagnostic value parameters of the 4 types of PTP scores for DVT are presented in Table 4. Figure 1 presents the ROC

Table 4. Diagnostic Value Parameters of the 4 Types of PTP Score.[a]

PTP Score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Wells score	47.5[b]	91.1	74.0[c]	76.4[d]
St Andre score	11.7	97.3[e]	70	67.3
Kahn score	21.7	97.5[e]	85.5[f]	69.8
Constans score	28.8	90.8	62.7	70.4

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PYP, pretest probability.
[a]All 4 PTP score scales were taken 2 or greater as the diagnostic point.
[b]Sensitivity: significantly higher than St Andre score, Kahn score, and Constans score, P < .001.
[c]Significantly higher than Constans score, P = .004.
[d]NPV: significantly higher than St Andre score, Kahn score, and Constans score, P < .01.
[e]Specificity: significantly higher than Wells score and Constans score, P < .001.
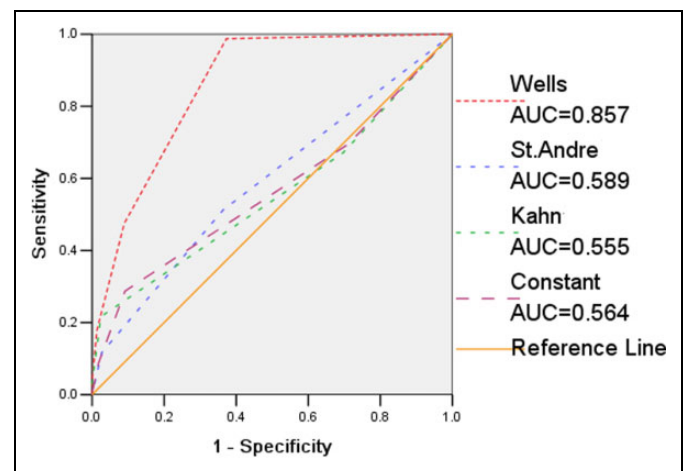[f]PPV: significantly higher than Constans score, P = .01.

Figure 1. The ROC curve of the 4 PTP scores for the diagnosis of DVT. DVT indicates deep venous thrombosis; PTP, pretest probability; ROC, receiver–operator characteristic.

curve of the 4 PTP scores for the diagnosis of DVT. The AUC of the Wells score was significantly larger compared to the other 3 scores (P < .05).

The Diagnostic Value Analysis of D-dimer Detections and Age-Adjusted Cutoff Values for DVT

The diagnostic value analysis of the 2 D-dimer detection systems and the age-adjusted cutoff value for DVT are presented in Table 5. Figure 2 presents the ROC curves of the D-Dimer Plus, Innovance D-Dimer, and age-adjusted cutoff value for DVT.

Diagnostic Value Analysis of the 4 Types of PTP Scores Combined With D-Dimer Detections

Table 6 presents the diagnostic value analysis of the 4 types of PTP scores in combination with D-dimer detection. The diagnostic value analyses of the D-dimer detection systems in combination with PTP scores, including sensitivity, specificity,

Table 5. The Diagnostic Efficacy of The 2 D-dimer Detections at Their Respective Diagnostic Points for DVT.

	Diagnostic Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
D-Dimer Plus	130 μg/L	95.8	13.6	37.3	85.9
Innovance D-Dimer	500 μg/L FEU	98.8	53.6[a]	53.3[b]	98.8[c]
Innovance D-Dimer with age-adjusted cutoff value	98.8	71.2[d]	64.8[e]	99.1[c]

Abbreviations: DVT, deep venous thrombosis; NPV, negative predictive value; PPV, positive predictive value.
[a]Sensitivity, significantly higher than D-Dimer Plus, *P* < .001.
[b]PPV: significantly higher than D-Dimer Plus, *P* < .001.
[c]NPV: significantly higher than D-Dimer Plus, *P* < .001
[d]Specificity: significantly higher than both D-Dimer Plus and Innovance D-Dimer, *P* < .001.
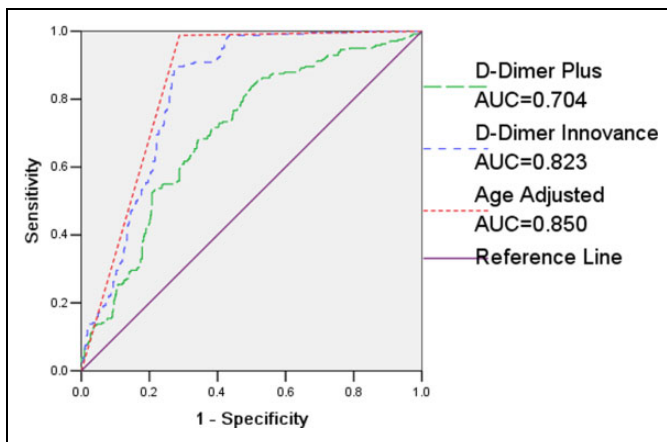[e]PPV: significantly higher than D-Dimer Plus and Innovance D-Dimer, *P* < .001.

Figure 2. Receiver–operator characteristic curve of the D-Dimer plus, Innovance D-Dimer, and age-adjusted cutoff value for DVT. DVT indicates deep venous thrombosis.

PPV, and NPV, are presented Table 6. When the sensitivity and the PPV were calculated, a positive for either the D-dimer or Wells score was considered positive. Regarding the specificity and NPV, only negative values for both parameters were considered negative.

Discussion

Pretest probability score is a diagnostic strategy designed for patients with suspected DVT to improve the efficacy of the clinical diagnosis of DVT. The possibility of DVT is based on clinical scores by quantifying the history, signs, and symptoms of each patient with suspected DVT. If the score is low, the patient is less likely to develop DVT. However, a high score indicates that the possibility is higher. Currently, commonly used PTP scores throughout the world include Wells score (9 quantitative indicators), St Andre score (6 quantitative indicators), Kahn score (4 quantitative indicators), and Constans score (6 quantitative indicators). Many foreign studies have confirmed that these clinical scores have important clinical value for reducing invasive examinations and medical expenses.[5-11] At present, the Wells score is widely used in clinical applications in China. However, the applicability of other PTP scores among the Chinese population is rarely reported.

Table 1 demonstrates that although the number of quantitative indicators of the 4 PTP scores differed, the scoring items exhibited numerous similarities, and each type of score had its own emphasis. As demonstrated in Table 2, most of the quantitative indicators involved in the 4 PTP scores were significantly different in DVT versus non-DVT, indicating that most of these scores exhibited good indicative function for the diagnosis of DVT.

All the PTP scores of 688 patients with suspected DVT are listed in Table 3. Although a relatively increased number of patients diagnosed as non-DVT were included in high probability group (n = 40), the total number of diagnosed patients with DVT based on the Wells score was considerably larger compared to the other 3 PTP scores. In addition, although a relatively small number of patients with relatively high scores were diagnosed as non-DVT, fewer patients were diagnosed as DVT with the St Andre score, Kahn score, and Constans score given the reduced number of quantitative indicators. Correspondingly, as noted in Table 4, although the St Andre score, Kahn score, and Constans score exhibited relatively increased specificity and PPV, the sensitivities were quite low, which significantly affected their clinical application. This finding explained why the AUC of the Wells score in Figure 1 was considerably increased compared to the other 3 (*P* < .01). In summary, among the 4 PTP scores, the Wells score had the best diagnostic efficacy for patients with suspected DVT.

Of note, although the AUC of the Wells score was the largest, the remaining 3 PTP scores were not useless. Given that the sensitivity, specificity, PPV, and NPV of these 4 types of PTP scores were different, attention should be given to the conjoint analysis in clinical application. For example, a patient diagnosed with a high possibility of DVT with the Kahn score may be considered to exhibit a low possibility of DVT with the Constans score. In consideration of the high specificity and PPV of the Kahn score, this patient is likely to be diagnosed with DVT by the Kahn score but misdiagnosed by the Constans score.

In general, the PTP score has high specificity and PPV for the diagnosis of DVT. However, given its lower sensitivity and NPV, it is necessary to combine this score with other indicators that possess increased sensitivity and NPV, such as serum D-dimer. Given that current commercial reagents react differently to the D-dimer fragments, the detection results of D-dimer

Table 6. Diagnostic Values of the D-Dimer Detections in Combination With PTP Scores.

	Types of PTP Scores	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
D-Dimer Plus	Wells	97.5	13.6	73.3[a]	91.0
	St Andre	95.8	13.6	70.0[a]	91.0
	Kahn	97.1	13.4	81.7[a]	88.2
	Constans	97.5	13.4	61.9[a]	90.9
Innovance D-Dimer	Wells	98.8	49.8	83.2[b,c]	98.7
	St Andre	98.8	52.9	75.7[b]	98.8
	Kahn	99.2	53.1	85.0[b,c]	99.2
	Constans	99.2	50.7	70.8[b]	99.1
Innovance D-Dimer with age-adjusted cutoff value	Wells	98.8	66.7[d]	85.1	99.0
	St Andre	98.8	70.3[d]	77.8	99.1
	Kahn	99.2	70.1[d]	89.5	99.4
	Constans	99.2	65.8[d]	80.0[e]	99.3

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PYP, pretest probability.
[a] PPV significantly higher than D-Dimer Plus, $P < .001$.
[b] Specificity: significantly higher than Innovance D-Dimer, $P < .001$.
[c] PPV: significantly higher than age-adjusted cutoff value $P < .001$.
[d] Specificity: significantly higher than Innovance D-Dimer in combination with PTP scores, $P < .001$
[e] PPV: significantly higher than D-Dimer Plus and Innovance D-Dimer, $P < .001$.

by different manufacturers are not universal. Therefore, no reference method is available for the detection of D-dimer.[6] Our hospital originally used the detection method of D-Dimer Plus and later introduced the Innovance D-Dimer, which is supported with better evaluation in the literature. In recent years, some literature proposed a method of adjusting the cutoff value based on age. Hence, this study aimed to compare these 3 D-dimer detection methods for the diagnosis of DVT. As shown in Table 5, the D-Dimer Plus had a sensitivity of 95.8% and an NPV of 85.9%, but the specificity and PPV were both relatively low at 13.6% and 37.3%, respectively. When the D-Dimer Plus was exclusively used as a screening index for DVT, there was a higher false-positive (FP) rate and a lower diagnostic efficacy with an AUC = 0.704. Compared to D-Dimer Plus, all the indicators of Innovance D-Dimer, including specificity (53.6%), PPV (53.3%), and NPV (99.1%), were significantly higher ($P < .001$) with the exception of the sensitivity (98.8%). Thus, its diagnostic efficacy was relatively increased with an AUC = 0.823. In addition, after adjusting the cutoff value by age, there was no significant change in sensitivity (98.8%) and NPV (99.1%); however, both the specificity and PPV were significantly increased, reaching 71.2% and 64.8%, respectively ($P < .001$), with AUC = 0.850.

The combination of age-adjusted cutoff value and Innovation D-Dimer is better for the diagnosis of DVT. What is the diagnostic efficacy of serum D-dimer testing in combination with the PTP scores?

In view of the fact that D-dimer has high FPs and false negatives, D-dimer is generally not used as an exclusive method for DVT diagnosis when it is marked as "likely to DVT" in PTP scores.[6,7] Therefore, in the parallel model of D-dimer and PTP scores for DVT diagnosis, namely, when the sensitivity and PPV were calculated, a positive score for either the D-dimer or PTP scores was considered a positive result. In contrast, when the specificity and NPV were calculated, both

negative indicators were considered negative. We also listed the sensitivity and PPV calculated with double positives. As shown in Table 6, the diagnostic efficacy of DVT diagnosis was significantly improved using the parallel model of serum D-dimer and PTP scores. If using a single or 2 positives as an indicator for DVT diagnosis, the sensitivity of D-Dimer Plus increased from 95.8% to 97.5% after combining it with Wells/Constans scores. However, the difference was not significant. However, if only both indicators were positive for DVT diagnosis, the PPV was significantly increased from 37.3% to 73.3% ($P < .001$). Compared with its use alone, the Innovance D-dimer combined with PTP scores showed no significant improvement in sensitivity, specificity, and NPV. Only the PPV of the double-positive indicator was increased from 53.3% to 70.8%-85.0% ($P < .01$). Furthermore, with regard to the age-adjusted cutoff value in D-dimer detection, the Innovance D-Dimer + Wells/Kahn's PPV was significantly increased compared to the age-adjusted D-dimer cutoff value ($P < .01$), whereas none of the other data were superior to the age-adjusted D-dimer cutoff value. In contrast, the specificity of the age-adjusted D-dimer cutoff value in combination with PTP score was significantly increased compared to either D-Dimer Plus or Innovance D-Dimer in combination with PTP score, reaching 65.8% to 70.3% ($P < .001$). However, the specificity was still less than that of the Innovance D-Dimer + age-adjusted cutoff value model, but the difference was not significant.

There are a few points worth noting. On one hand, given its low specificity, the D-dimer Plus exhibits an increased possibility of FPs. When the D-dimer Plus was incorporated with PTP scores, the specificity was not significantly improved when using the double negative as the exclusion criterion. This finding is consistent with those reported in the literature. For instance, Fronas et al reported that the specificity of D-Dimer Plus was 40.3% and decreased to 36.6% when combined with

Wells score.[17] In contrast, the PPV is significantly improved up to 61.9% to 81.7% using double-positive results as inclusion criteria. However, given the relatively low proportion of double-positive results in suspected patients, a considerable number of patients who had only one positive indicator remained after further exclusion. Analogously, although the NPV was improved by using the double-negative exclusion criteria, the improvement was not significant. Given the relatively low proportion of double negatives in suspected patients, a considerable number of patients with only one negative still remained after further exclusion. On the other hand, Innovance D-Dimer in combination with age-adjusted cutoff values can provide better diagnostic performance data with increased sensitivity, specificity, and NPV. Compared with the Innovance D-Dimer + age-adjusted cutoff value model, only the PPV was significantly increased in the Innovance D-Dimer + PTP scores model. However, as the proportion of double positives in suspected patients was comparatively reduced, the PPV of the Innovance D-Dimer + PTP scores model ranged from 70.8% to 85.0%. Hence, it was still difficult to exclude the FP situation. Thus, these data were impractical in clinical application. In addition, the specificity of Innovation D-Dimer + age-adjusted cutoff value + PTP scores was almost the same as the Innovance D-Dimer + age-adjusted cutoff value model. These findings indicated that the use of the Innovance D-Dimer in combination with the age-adjusted cutoff value for the diagnosis of DVT can achieve relatively high sensitivity and NPV and that this model exhibits equivalent diagnostic efficacy as the Innovance D-Dimer in combination with PTP scores.

Pretest probability scores are useful in judging the possibility of DVT, which requires subjective judgment and clinical experience. D-Dimer combined with age-adjusted cutoff value is a relatively simple and objective method in clinical work. In addition, according to the literature reports, D-Dimer plays an important role in prognostic evaluation for various diseases, including digestive tract tumors, ovarian cancer, lung cancer, lymphoma, and cerebral hemorrhage. Even if the patient does not have DVT, the D-Dimer level remains useful in prognosis evaluation.[18-27] Therefore, compared to the complex and subjective PTP score, it is simpler and more practical to use Innovance D-Dimer combined with age adjustment cutoff value to judge the possibility of DVT in clinical work.

In summary, Wells score exhibited the best diagnostic efficacy for our patients with suspected DVT among the 4 PTP scores. Innovance D-Dimer in combination with age-adjusted cutoff values exhibited high sensitivity and NPV for DVT diagnosis and was equivalent to the diagnostic efficacy of the Innovance D-Dimer in combination with PTP scores. This technique is simpler and more practical in daily work.

Authors' Note

Junxun Li and Fan Zhang contributed equally to this study and should be considered as co-first author. J. Li and F. Zhang collected and analyzed data and drafted the manuscript. F. Zhang, Z. Ye, and C. Liang recruited patients. F. Zhang, Z. Ye, and S. Chen performed the tests. J. Li and Z. Ye contributed to study design. J. Li and C. Liang drew the conclusions and wrote the manuscript. All authors approved the manuscript. Ethical approval to report this case was obtained from ethics committee of First Affiliated Hospital of Sun Yat-sen University.

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