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Diagnostic Value of the Padua Score Combined with Thrombotic Biomarker Tissue Plasminogen Activator Inhibitor-1 (tPAI-1) Detection for the Risk of Deep Vein Thrombosis in Patients with Pulmonary Heart Disease

Xiaoyun Zhang*, Xinlong Xi, Wenming Bian, Qiang Liu

Department of Cardiovascular Medicine, People's Hospital of Pengzhou, Pengzhou 611930, Sichuan Province, China

Corresponding author: **Xiaoyun Zhang,** 656042672@qq.com

Abstract: This study explores the diagnostic value of combining the Padua score with the thrombotic biomarker tissue plasminogen activator inhibitor-1 (tPAI-1) for assessing the risk of deep vein thrombosis (DVT) in patients with pulmonary heart disease. These patients often exhibit symptoms similar to venous thrombosis, such as dyspnea and bilateral lower limb swelling, complicating differential diagnosis. The Padua Prediction Score assesses the risk of venous thromboembolism (VTE) in hospitalized patients, while tPAI-1, a key fibrinolytic system inhibitor, indicates a hypercoagulable state. Clinical data from hospitalized patients with cor pulmonale were retrospectively analyzed. ROC curves compared the diagnostic value of the Padua score, tPAI-1 levels, and their combined model for predicting DVT risk. Results showed that tPAI-1 levels were significantly higher in DVT patients compared to non-DVT patients. The Padua score demonstrated a sensitivity of 82.61% and a specificity of 55.26% at a cutoff value of 3. The combined model had a significantly higher AUC than the Padua score alone, indicating better discriminatory ability in diagnosing DVT risk. The combination of the Padua score and tPAI-1 detection significantly improves the accuracy of diagnosing DVT risk in patients with pulmonary heart disease, reducing missed and incorrect diagnoses. This study provides a comprehensive assessment tool for clinicians, enhancing the diagnosis and treatment of patients with cor pulmonale complicated by DVT. Future research should validate these findings in larger samples and explore additional thrombotic biomarkers to optimize the predictive model.

Keywords: Padua prediction score; Tissue plasminogen activator inhibitor-1 (tPAI-1) detection; Deep vein thrombosis (DVT); Pulmonary heart disease (cor pulmonale); Diagnostic accuracy

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1. Introduction

Venous thrombosis is a common disease, encompassing deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) [1-4]. Clinically, DVT patients typically present with calf swelling, local pain, and

tenderness, while patients with pulmonary embolism often experience symptoms such as dyspnea, chest tightness, and hemoptysis [5,6]. The most significant causes of this disease include high blood viscosity, slow blood flow, and damage to the vessel wall. In recent years, medical staff have increased their focus on DVT, and there has been significant progress in its diagnosis and treatment. However, the incidence rate continues to rise [6,7]. Due to the lack of specificity in the clinical symptoms, signs, and laboratory tests for DVT, nearly half of DVT patients lack typical symptoms and signs such as lower limb swelling and/or pain, making diagnosis and treatment more difficult and prone to missed or incorrect diagnoses [8]. Approximately 60% of untreated DVT patients may experience fatal pulmonary embolism due to thrombus detachment.

Patients with chronic pulmonary heart disease often present with right heart failure and systemic venous congestion as primary manifestations, with many experiencing dyspnea and bilateral lower limb swelling. These symptoms overlap with those of venous thrombosis, complicating differentiation. Data indicate that autopsy findings show a pulmonary thromboembolism incidence rate of 10.9%-53% in patients with pulmonary heart disease [9,10]. Pulmonary embolism often progresses from lower limb venous thrombosis. Patients with chronic pulmonary heart disease are prone to chronic hypoxia, acidosis, and endotoxin damage to the vascular endothelium during infections, promoting platelet aggregation and microthrombosis formation [11,12]. Chronic hypoxia induces excessive secretion of erythropoietin, leading to increased red blood cell production, resulting in increased blood viscosity and a hypercoagulable state. Increased blood viscosity, compensatory increase in cardiac output, and pulmonary hypertension increase the preload and afterload of the right heart, impairing its blood storage and pumping functions, causing right heart dysfunction and right heart failure, leading to systemic venous congestion and slow blood flow. Additionally, patients with chronic pulmonary heart disease often have respiratory failure and impaired lung function, with limited activity, making them prone to deep vein thrombosis in the lower limbs [12,13].

The Padua Prediction Score is a risk assessment model used to identify hospitalized medical patients at risk for venous thromboembolism (VTE). It is recommended by guidelines for all hospitalized medical patients to evaluate their risk of developing VTE. The score is calculated based on several clinical factors, with each factor assigned a specific point value. A total score of 4 or more indicates a high risk of VTE, while a score below 4 suggests a low risk [14,15]. Tissue plasminogen activator inhibitor-1 (tPAI-1) is a primary fibrinolytic system inhibitor secreted by endothelial cells, platelets, and hepatocytes. It regulates fibrin degradation by inhibiting plasminogen activators, affecting thrombus formation. High tPAI-1 levels indicate increased VTE risk, aiding in diagnosis, risk assessment, and guiding personalized treatment [16,17]. This study retrospectively analyzed the clinical data of hospitalized patients with cor pulmonale, using the receiver operating characteristic (ROC) curve to compare the Padua score, tPAI-1, and their combined model for predicting the risk of DVT in the lower limbs. The area under the curve (AUC) was used to explore their diagnostic value for cor pulmonale complicated with DVT.

2. Materials and methods

2.1. General information

The study subjects were patients with suspected lower extremity DVT and cor pulmonale treated at our hospital from January 2022 to December 2023. Inclusion criteria were based on the 2018 guidelines for diagnosing and treating chronic pulmonary heart disease. Patients needed to meet any one of the following conditions: a history of COPD, chronic bronchitis, emphysema, or other chest and lung diseases (primary pulmonary vascular diseases such as idiopathic pulmonary hypertension, thromboembolic pulmonary hypertension may not have this history); experiencing dyspnea, fatigue, and reduced exercise tolerance; signs of elevated pulmonary artery pressure, right ventricular enlargement, or right heart failure such as jugular venous distension, P2 > A2,

enhanced cardiac impulse below the xiphoid process, hepatomegaly with tenderness, positive hepatojugular reflux, and lower extremity edema; signs suggestive of cor pulmonale on ECG or chest X-ray; echocardiography indicating widened pulmonary artery and right ventricular enlargement or hypertrophy. Diagnosis of chronic pulmonary heart disease requires meeting any one of the first four criteria and the fifth criterion and excluding other diseases causing right heart changes (e.g., rheumatic heart disease, cardiomyopathy, congenital heart disease). Additionally, suspected DVT patients were selected according to the Chinese Medical Association's Vascular Surgery Group's "Guidelines for the Diagnosis and Treatment of Deep Vein Thrombosis (Third Edition)" if they met any of the following conditions: lower extremity tenderness, swelling, positive Homan's sign, varicose veins, localized skin temperature increase, or D-dimer > 0.55 mg/L. Exclusion criteria included not completing the clinical scoring scales and lower limb vascular color Doppler ultrasound, CT, or venography within 48 hours before or after admission; having received simple anticoagulation or intravenous thrombolytic therapy in another hospital or outpatient setting before admission; and being under 18 years of age. This study adheres to the principles of the Declaration of Helsinki.

2.2. Scoring system and sample collection

(1) Padua scoring system: The Padua scoring system was performed independently by two physicians based on the clinical data of the study subjects. The details of the Padua scoring system are listed in **Table 1**. In case of disagreement, a senior physician re-evaluated.

(2) Diagnosis criteria for venous thromboembolism (VTE): Referencing the 2008 guidelines for the diagnosis and treatment of VTE, clinical symptoms and physical signs suggesting deep vein thrombosis (DVT) of the lower extremities include: incomplete compression of the veins shown by compression ultrasound.

(3) Data collection indicators: All group patients' basic information (age, gender, comorbidities, blood glucose, lipids, liver function), new biomarkers, and Padua scores were collected. Blood samples were collected from the antecubital vein of fasting patients into blue-capped tubes containing 3.2% sodium citrate anticoagulant, centrifuged, and the plasma stored at -80°C. Biomarkers, including tissue-type plasminogen activator inhibitor-1 (tPAI-1) complex, were measured using ELISA, with testing and data analysis blinded to avoid bias.

Table 1. Padua scoring system evaluation

Risk factors	
Active malignant tumor, with metastasis and/or treated within the last 6 months with chemotherapy or radiotherapy	3
Previous venous thromboembolism	3
Immobilization, due to medical or physical reasons, for ≥ 3 days	3
Inherited or acquired thrombophilia (e.g., protein C or S deficiency, Leiden factor V, prothrombin G20210A mutation, or antiphospholipid antibody syndrome)	3
Recent (≤ 1 month) trauma or surgery	2
Age ≥ 70	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disease	1
Obesity (BMI ≥ 30 kg/m^2)	1
Ongoing hormonal treatment	1

2.3. Statistical analysis

Data were analyzed using StataSE-64 statistical software. Measurement data not conforming to a normal distribution were expressed as median (interquartile range) and analyzed using the non-parametric rank-sum test. Categorical data were expressed as percentages (%) and analyzed using the Chi-squared test. To evaluate the diagnostic value of the Padua scoring system and novel serum thrombosis biomarkers for cor pulmonale complicated with DVT, receiver operating characteristic (ROC) curves were constructed. True positive rate, true negative rate, Youden index, optimal cut-off points, and AUC were calculated for individual and combined assessments of the Padua score and novel coagulation molecular markers in predicting DVT risk in cor pulmonale. Univariate and logistic regression analyses were performed on the Padua score, novel serum thrombosis biomarkers, and other clinical data of the patients. A *P*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Baseline data of patients

The clinical indicators and test results of the patients are shown in **Table 2**. The tPAI-1 levels were higher in the DVT group compared to the non-DVT group, with a median (interquartile range) of 42.2 (72.6) ng/mL versus 29.8 (62) ng/mL. The difference was statistically significant ($Z = -5.012$, $P < 0.001$). The demographic data, pulmonary comorbidities, clinical symptoms, physical examination results, and pulmonary function test results showed no statistically significant differences between the two groups (*P* values > 0.05).

Table 2. Baseline data of patients with and without deep vein thrombosis (DTV)

Item	Without DTV (*n* = 67)	With DTV (*n* = 56)	Statistical value	*P* value
Male [*n* (%)]	45 (67.16)	30 (53.57)	$\chi^2 = 0.025$	0.874
Age (years), [M (QR)]	73 (19.5)	76 (12.5)	$Z = -1.488$	0.137
BMI (kg/m) [mean ± SD]	25.21 ± 4.39	25.87 ± 4.49	$t = -0.772$	0.441
Bedridden time ≥ 3 days [*n* (%)]	9 (13.43)	11 (19.64)	$\chi^2 = 2.841$	0.092
Catheterization [*n* (%)]	19 (28.36)	13 (23.21)	$\chi^2 = 0.415$	0.519
COPD [*n* (%)]	31 (46.27)	21 (37.50)	$\chi^2 = 0.428$	0.514
Bronchiectasis cases [*n* (%)]	9 (13.43)	11 (19.64)	$\chi^2 = 1.984$	0.159
Primary lung cancer [*n* (%)]	15 (22.39)	14 (25.00)	$\chi^2 = 0.462$	0.497
Interstitial lung disease [*n* (%)]	7 (10.45)	6 (10.71)	$\chi^2 = 0.162$	0.688
Cough, expectoration [*n* (%)]	57 (85.07)	40 (71.43)	$\chi^2 = 3.107$	0.078
Wheezing [*n* (%)]	14 (20.90)	12 (21.43)	$\chi^2 = 0.007$	0.933
Breathing difficulties [*n* (%)]	36 (53.73)	30 (53.57)	$\chi^2 = 0.042$	0.838
Chest pain [*n* (%)]	8 (11.94)	7 (12.50)	$\chi^2 = 0.108$	0.743
Hemoptysis [*n* (%)]	2 (2.99)	2 (3.57)	$\chi^2 = 0.013$	0.909
Fever [*n* (%)]	7 (10.45)	6 (10.71)	$\chi^2 = 0.953$	0.329
Pulmonary artery hypertrophy or triple branch enlargement [*n* (%)]	17 (25.37)	14 (25.00)	$\chi^2 = 0.082$	0.774
Heart rate (X/min) [mean ± SD]	79.88 ± 16.82	81.04 ± 17.05	$t = -0.376$	0.708
Lower limb swelling [*n* (%)]	15 (22.39)	17 (30.36)	$\chi^2 = 1.859$	0.173

(Continued Table 2)

Unilateral limb pain [*n* (%)]	7 (10.45)	3 (5.36)	$\chi^2 = 1.004$	0.317
tPAI levels (ng/mL) [M (QR)]	29.8 (62)	42.2 (72.6)	Z = -2.741	0.006
PaO_2 (mmHg) [mean ± SD]	68.51 ± 16.71	63.70 ± 12.50	$t = 1.749$	0.081
D_LCO SB % pred [mean ± SD]	48.30 ± 22.18	47.58 ± 18.42	$t = 0.156$	0.876
D_LCO/VA % pred [mean ± SD]	71.99 ± 27.75	70.77 ± 20.01	$t = 0.176$	0.861

3.2. Predictive value of the Padua score for DTV

Using the Padua score for clinical assessment, patients were categorized into low-risk and high-risk groups, with 72 and 51 patients respectively. Among these, 21 patients in the low-risk group and 35 patients in the high-risk group were diagnosed with DVT. The diagnosis rates were approximately 29.17% for the low-risk group and 68.63% for the high-risk group ($\chi^2 = 18.74$, $P < 0.001$).

3.3. ROC curve for diagnosing DTV using Padua score and tPAI-1 levels

When the cutoff value for Padua is set to 3, the model's sensitivity is 0.8261, specificity is 0.5526, and Youden's Index is 0.3787. Specifically, the model can successfully identify approximately 82.61% of actual positive samples and about 55.26% of actual negative samples. The Youden's Index, which combines sensitivity and specificity, is 0.3787, indicating that the overall classification performance of Padua at this cutoff value is relatively moderate. These results provide important references for further optimization and selection of an appropriate model.

In comparing the AUC values of the models, we found that the combined model (tPAI-1 and Padua) had a significantly higher AUC (0.9192) than the Padua model alone (0.7683), with a corresponding Z value of 2.59 and a two-sided P value of 0.0192. This indicates that the performance of the combined model is significantly superior to the Padua model alone, with a higher discriminatory ability. Additionally, when comparing the AUC values of the combined model (tPAI-1 and Padua) to tPAI-1 alone, although the combined model's AUC (0.9192) was higher than that of tPAI-1 (0.8528), the corresponding Z value was 1.30, with a two-sided *P* value of 0.1936. This suggests that the performance difference between the combined model and tPAI-1 alone is not significant, and both have relatively similar discriminatory abilities (**Figure 1**).

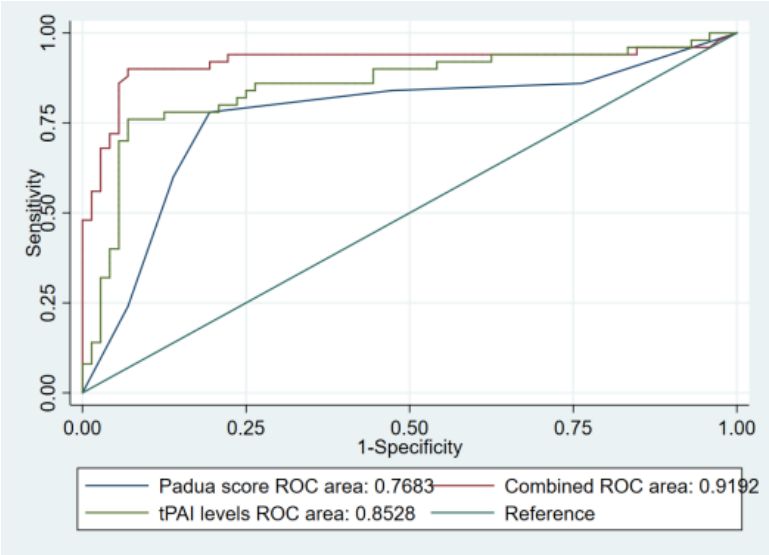

Figure 1. ROC curve for diagnosing DTV using Padua score and tPAI-1 levels

These findings highlight the effectiveness of combining tPAI and Padua scores for enhanced diagnostic accuracy, while also indicating areas for potential improvement and further model optimization.

4. Discussion

This study investigates the diagnostic value of the Padua score combined with the novel thrombotic biomarker, tissue plasminogen activator inhibitor-1 (tPAI-1), for predicting the risk of DVT in patients with pulmonary heart disease (cor pulmonale). This combination aims to enhance diagnostic accuracy and address the limitations of individual assessment methods.

4.1. Diagnostic challenges in cor pulmonale patients

Patients with chronic pulmonary heart disease frequently present with symptoms that overlap with those of venous thrombosis, such as dyspnea, bilateral lower limb swelling, and signs of right heart failure. These overlapping symptoms make it challenging to differentiate between the conditions based solely on clinical presentation and traditional diagnostic methods. Consequently, there is a significant risk of missed or incorrect diagnoses, which can lead to fatal pulmonary embolism in untreated DVT patients.

4.2. Padua score and tPAI-1

The Padua Prediction Score is a widely used risk assessment tool that evaluates the likelihood of VTE based on clinical factors. However, its specificity and sensitivity in chronic pulmonary heart disease patients need improvement due to the nonspecific symptoms of DVT in these patients. Tissue plasminogen activator inhibitor-1 (tPAI-1) is a biomarker that inhibits fibrinolysis and is indicative of a hypercoagulable state, thus serving as a potential diagnostic tool for DVT.

The study retrospectively analyzed clinical data from patients with cor pulmonale to evaluate the effectiveness of the Padua score and tPAI-1 levels in diagnosing DVT. Key findings include the following:

(1) Patients with DVT exhibited significantly higher tPAI-1 levels compared to those without DVT, suggesting that higher tPAI-1 levels correlate with an increased risk of DVT.

(2) The Padua score demonstrated moderate diagnostic accuracy with a sensitivity of 82.61% and specificity of 55.26% at a cutoff value of 3.

(3) The combination of the Padua score and tPAI-1 levels significantly improved diagnostic accuracy, with the combined model showing a higher area under the curve (AUC) compared to the Padua score alone. This indicates better discriminatory ability, making it a more reliable tool for diagnosing DVT in cor pulmonale patients.

The findings highlight the importance of integrating multiple diagnostic approaches to improve the accuracy of DVT diagnosis in patients with chronic pulmonary heart disease. The combined use of the Padua score and tPAI-1 levels offers a more comprehensive assessment, potentially reducing the incidence of missed or incorrect diagnoses and enabling timely and appropriate treatment.

Further research should focus on validating these findings in larger, prospective cohorts and exploring additional biomarkers that may complement the Padua score and tPAI-1 levels. Developing more sophisticated models incorporating these biomarkers could enhance predictive accuracy and clinical utility, ultimately improving patient outcomes.

The study demonstrates that combining the Padua score with thrombotic biomarker tPAI-1 detection

significantly enhances the diagnostic accuracy for DVT risk in patients with cor pulmonale. This integrated approach addresses the limitations of individual diagnostic methods and offers a promising strategy for better managing and treating this high-risk patient population.

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Disclosure statement

The authors declare no conflict of interest.

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