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Original Article

Risk factors for pulmonary embolism in malignant tumors patients with lower limb deep vein thrombosis: a retrospective study

Junfeng Li[1*], Zhen Li[2*], Hui Zheng[3], Yuan Gao[1]

[1]Department of Vascular Surgery, The Second Affiliated Hospital of Shandong First Medical University, Tai'an, Shandong, China; [2]Department of Oncology, The Second Affiliated Hospital of Shandong First Medical University, Tai'an, Shandong, China; [3]Department of Vascular Surgery, General Surgery Clinical Center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [*]Co-first authors.

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Abstract: Objective: To identify the risk factors associated with pulmonary embolism (PE) in malignant tumor patients with lower limb deep vein thrombosis (LLDVT). Methods: We retrospectively analyzed the clinical data of 45 patients with PE (observation group) and 255 patients without PE (control group) admitted to The Second Affiliated Hospital of Shandong First Medical University between June 2020 and January 2025. Various clinical parameters, including LLDVT density ratio, D-dimer, homocysteine (Hcy) and cardiac troponin I (cTNI), were compared between the two groups. Logistic regression analysis was performed to identify independent risk factors for PE. Results: The observation group had significantly higher values for LLDVT density ratio (P<0.001), D-dimer (P=0.004), Hcy (P<0.001), cTNI (P<0.001), and Wells scores (P<0.001) compared to the control group. Logistic regression revealed that LLDVT density ratio, Hcy, cTNI, and Wells scores were independent risk factors for PE in these patients. Pearson correlation analysis showed significant positive associations between the LLDVT density ratio (r=0.822, P<0.001), Hcy (r=0.899, P<0.001), cTNI (r=0.890, P<0.001), and Wells scores. ROC curve analysis indicated that the combined model (LLDVT density ratio, Hcy, and cTNI) had a higher AUC (0.852) than individual markers. Conclusion: LLDVT density ratio, Hcy, and cTNI are independent predictors of PE in malignant tumor patients with LLDVT. These markers are closely associated with PE severity, which could assist in optimizing clinical management for these patients.

Keywords: Pulmonary embolism, malignant tumor, lower limb deep vein thrombosis, risk factor

Introduction

Pulmonary embolism (PE) is a potentially fatal condition, characterized by partial or complete obstruction of the pulmonary arterial bed due to thrombotic emboli. It has become the third leading cause of cardiovascular morbidity and mortality [1]. Cancer patients are particularly at risk for PE. Previous studies have reported that the incidence of PE in patients with malignancies ranges from 3.1% to 9%, and the link between malignancy and PE is well established [2, 3]. PE is a major cause of death in cancer patients, largely attributed to biological factors and the cancer care process. Studies have shown that neoplastic cells in cancer patients release pro-inflammatory mediators and procoagulant proteins, leading to a hypercoagulable state [4]. Additionally, indirect factors such as vascular injury and hypercoagulation are commonly observed in patients with malignancies [5]. For most cancer patients, the occurrence of PE is associated with blood clots that dislodge from the walls of veins in deep vein thrombosis (DVT) and travel to the pulmonary arteries via the heart [6]. Thus, patients with malignant tumors represent a unique and vulnerable subgroup of PE patients.

Given the fatal consequences and frequency of PE, prompt diagnosis is crucial. However, PE is challenging to diagnose clinically due to the non-specificity of its signs and symptoms. Symptoms such as chest pain, palpitations,

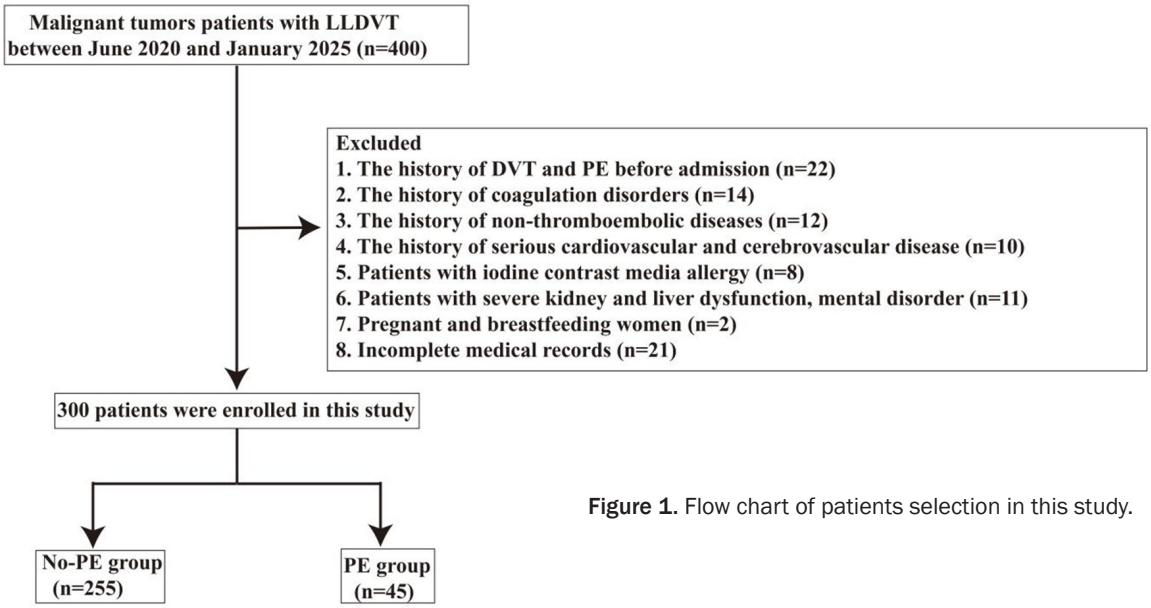

Figure 1. Flow chart of patients selection in this study.

chest tightness, dyspnea, and cough with blood in sputum may be misdiagnosed as chronic pulmonary heart disease, coronary heart disease, or acute exacerbations of chronic obstructive pulmonary disease, which contributes to the high mortality rate of PE [7, 8]. Several non-invasive prediction models, including the widely used Wells score, have been developed for PE diagnosis, but they still carry a risk of misdiagnosis or missed diagnosis when relied upon alone [9]. Therefore, exploring new methods and diagnostic systems is essential.

Cancer patients are 2-4 times more likely to experience venous thromboembolism compared to those without malignancies [10]. Moreover, cancer patients with DVT are nearly twice as likely to develop PE compared to those without DVT [11]. Research indicates that thrombus detachment from lower limb deep vein thrombosis (LLDVT) is the primary source of PE, with approximately 90% of PE cases originating from DVT [12]. PE in cancer patients can be treated effectively with timely diagnosis and appropriate treatment. Thus, it is crucial to develop an effective risk evaluation method to facilitate early diagnosis and treatment of PE in these patients. However, there is limited research on PE risk prediction in cancer patients with DVT. This study aims to identify risk factors for PE in cancer patients with LLDVT. The findings will provide general recommendations for PE diagnosis in this patient population, highlight gaps requiring further investigation, and suggest factors that could contribute to the clinical management of these patients.

Materials and methods

General information

This retrospective study included 300 cancer patients with LLDVT who were treated at The Second Affiliated Hospital of Shandong First Medical University between June 2020 and January 2025 (**Figure 1**). These patients were divided into an observation group (n=45) and a control group (n=255) based on the presence of PE. Risk stratification of PE was based on hemodynamic status, right ventricular function, and myocardial injury markers, categorizing patients into high, moderate, and low-risk groups [13]. According to the guidelines for the diagnosis and treatment of PE [14], the observation group was further divided into low risk (n=15), moderate risk (n=18), and high risk (n=12).

The study was approved by the Ethics Committee of The Second Affiliated Hospital of Shandong First Medical University (No. 2025-360).

Inclusion criteria: (1) Age >18 years. (2) Diagnosis of LLDVT based on clinical and color Doppler ultrasonography [15], showing either

partial or complete venous compression. (3) Patients diagnosed and treated for common malignant tumors. (4) Diagnosis of PE confirmed by radiography or angiography, showing incomplete contrast filling in the pulmonary artery and vascular occlusion, with or without the tramline sign [16]. (5) First diagnosis of DVT and PE. (6) Complete medical records.

Exclusion criteria: (1) History of DVT or PE before admission. (2) History of coagulation disorders. (3) Coexisting severe cardiovascular or cerebrovascular diseases, such as myocardial infarction, heart failure, or atrial fibrillation. (4) Coexisting non-thromboembolic diseases, such as fat embolism or malignant tumor embolism. (5) Inability to undergo CT or contrast examination due to iodine contrast media allergy. (6) Severe kidney dysfunction (glomerular filtration rate <15 mL/min) or liver dysfunction (Child-Pugh Class C). (7) Presence of mental disorders. (8) Pregnancy or breastfeeding.

Data collection

Data were independently collected by two investigators, who resolved any discrepancies between them. A standardized form was used for data collection, ensuring the completeness of medical records and the consistency of diagnostic criteria.

General patient data were collected, including age, gender, body mass index (BMI), smoking, alcohol use, late-night habits, diabetes, hypertension, family history of venous thrombosis, infections, hyperlipidemia, coronary heart disease, arrhythmias, and chronic lung diseases. Clinical characteristics such as the side and location of DVT, disease course, tumor type, Caprini scores, DVT treatment methods, prolonged bed rest (>48 h), peripherally inserted central catheter (PICC) implantation, hospital surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, tumor staging, Wells scores, and LLDVT density ratio were also recorded.

Additionally, hematologic data obtained within 3 days of hospital admission, including white blood cells, monocytes, neutrophils, lymphocytes, hemoglobin, platelets, D-dimer, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, serum creatinine (Cr), C-reactive protein (CRP), homocysteine (Hcy), and cardiac troponin I (cTNI), were recorded. The following formulas were used based on previous reports [17]:

Systemic immune-inflammatory index (SII) = Platelet count × Neutrophil count/Lymphocyte count.

Neutrophil-to-lymphocyte ratio (NLR) = Neutrophil count/Lymphocyte count.

Platelet-to-lymphocyte ratio (PLR) = Platelet count/Lymphocyte count.

Outcomes measures

LLDVT density ratio: Contrast-enhanced CT (Siemens, Germany) was performed to scan the pulmonary artery and lower extremity veins using iodixanol (32 g/100 ml). The scanning parameters were: 120 kV tube voltage, 200 mAs current, 0.75 mm slice thickness, 1 mm interval, and a 150-second scanning delay for the lower extremity vein examination. The patient was positioned supine, with the scanning direction starting from the head. The patients were instructed to take a deep breath and hold it during the scan.

First, pulmonary artery angiography was performed, placing the region of interest on the pulmonary artery trunk and setting the threshold at 100 Hu. After this, a lower extremity venous scan was conducted. Contrast agent (2 mL/kg) was injected intravenously at a rate of 3.5 mL/s, and the scan began 3 minutes post-injection at the level of the third lumbar vertebra. After image acquisition, the CT value of thrombus was measured as the ratio of the CT value of the nearest filling defects in the vessel to the CT value of the contralateral normal vein. The formula for the LLDVT density ratio was: LLDVT density ratio = CT value of the nearest thrombus/CT value of the contralateral normal vein.

Wells scores: Wells scores are a well-established screening tool for PE. The following criteria were scored: (1) Clinical signs and symptoms of DVT (3 points). (2) Alternative diagnoses are less likely than PE (3 points). (3) Immobilization or surgery in the previous four weeks (1.5 points). (4) Previous history of PE or DVT (1.5 points). (5) Heart rate >100 beats/min (1.5 points). (6) Malignancy (1.0 points).

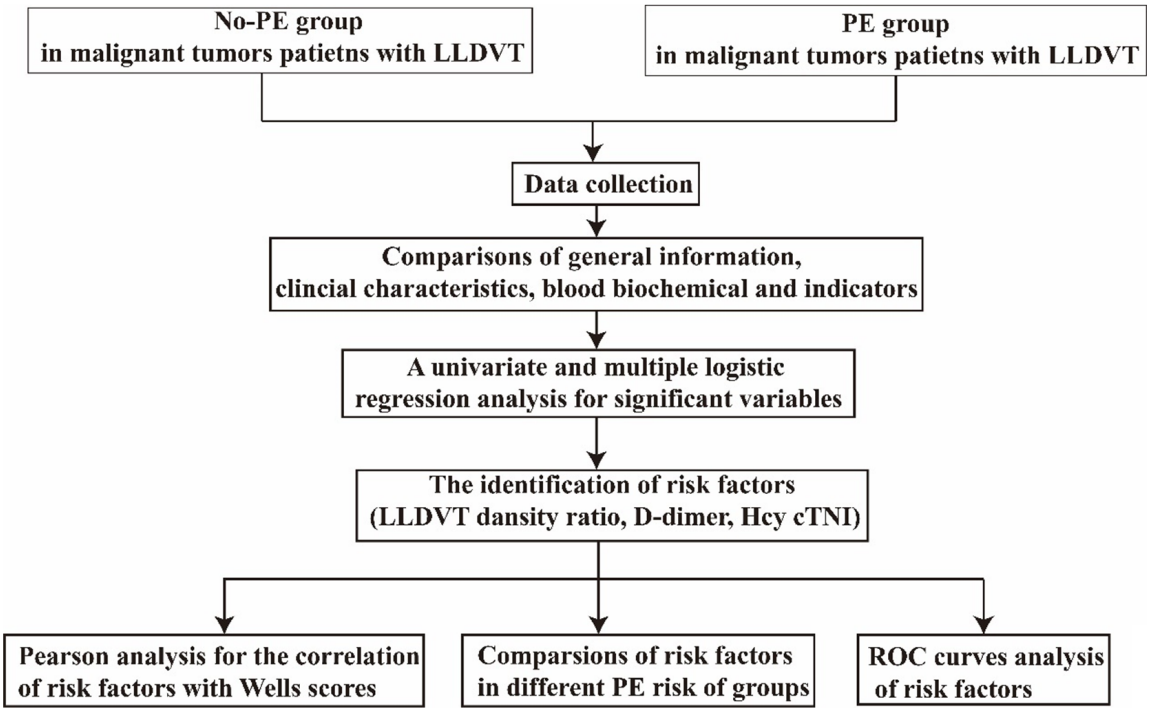

Figure 2. Flow diagram of study design in this study. Note: PE: Pulmonary embolism; LLDVT: Lower limb deep vein thrombosis; Hcy: Homocysteine; cTNI: Cardiac troponin I; AUC: Area under the curve; ROC: Relative operating characteristic.

(7) Hemoptysis (1.0 points). All patients in the observasion group were evaluated using the Wells score.

Blood biochemical indicators examination: Fasting peripheral venous blood was drawn in the morning. The collected blood was centrifuged at 2500 r/min for 10 minutes. The supernatant was used to measure the levels of cTNI and Hcy using a fully automated biochemical analyzer (AU5400, Olympus Corporation, Japan).

Statistical analysis

The data were analyzed using the SPSS 22.0 (IBM Corporation, USA). Continuous variables were presented as mean ± standard deviation (SD), and categorical data were presented as percentages (%)/number of cases. Comparisons between continuous data were performed using the independent t-test, and comparisons of categorical data were performed using the chi-square (χ^2) test. The relationship between significant variables and Wells scores was assessed using Pearson correlation analysis. Multiple logistic regression analysis using the forward likelihood ratio (LR) method was performed to identify risk factors for PE in malignant tumor patients with LLDVT. The predictive value of significant variables for PE, including specificity and sensitivity, was calculated based on previous studies [18]. The receiver operating characteristic (ROC) curve was used to evaluate the predictive ability of these variables with $P<0.05$ in multiple logistic regression. Comparisons of areas under the curves (AUCs) were performed using the DeLong test [19]. Statistical significance was set at $P<0.05$.

Results

Comparison of general information

The study design flow diagram is shown in **Figure 2**. As presented in **Table 1**, no significant differences were found between the control and observation groups in terms of age, gender, body mass index (BMI), smoking, alcohol consumption, late-night habits, diabetes, hypertension, family history of venous thrombosis, infections, hyperlipidemia, coronary heart disease, arrhythmia, or chronic lung diseases

Table 1. The comparison of general information between observation group and control group

Parameters	Control group (N=255)	Observation group (N=45)	t/χ^2	*P*
Age (years)	64.25±6.41	65.37±7.12	1.062	0.289
Gender (Male/Female)	165/90	32/13	0.696	0.404
BMI (kg/m^2)	22.39±2.68	22.74±2.81	0.802	0.423
Smoking (%)	63 (24.71%)	12 (26.67%)	0.078	0.779
Drinking (%)	50 (19.61%)	10 (22.22%)	0.163	0.686
Stay up late	86 (33.73%)	16 (35.56%)	0.057	0.811
Diabetes (%)	25 (9.80%)	5 (11.11%)	0.073	0.788
Hypertension (%)	100 (39.22%)	19 (42.22%)	0.145	0.704
Family history of venous thrombosis	2 (0.78%)	1 (2.22%)	0.799	0.371
Infections	76 (29.80%)	9 (20.00%)	1.811	0.178
Hyperlipaemia (%)	11 (4.31%)	3 (6.67%)	0.476	0.490
Coronary heart disease	3 (1.18%)	1 (2.22%)	0.318	0.573
Arrhythmia	4 (1.57%)	2 (4.44%)	1.614	0.204
Chronic lung diseases	38 (14.90%)	5 (11.11%)	0.448	0.503

Note: BMI: Body mass index.

(all P>0.05), indicating that the groups were comparable.

Comparison of clinical characteristics

The LLDVT density ratio in the control group was 39.78±9.65, while it was 49.92±10.58 in the observation group. A significant difference was found between the two groups (P<0.001). Additionally, the Wells score in the observation group was 5.68±0.97, significantly higher than that in the control group (3.19±0.87), with a clear statistical difference (P<0.001). However, no significant differences were observed in other clinical characteristics, such as the side and location of LLDVT, tumor course, tumor type, Caprini scores, DVT treatment methods, long-term bedridden status (>48 h), implantation of a PICC, hospital surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, and tumor staging, as shown in **Table 2**.

Comparison of blood biochemical indicators

As shown in **Table 3**, regarding blood biochemical indicators, D-dimer levels in the observation group were 4.08±1.21 mg/L, significantly higher than in the control group (3.55±1.13 mg/L, P=0.004). Hcy in the control group was 10.38±2.06 μmol/L, while in the observation group, it was 26.42±2.53 μmol/L, which was significantly higher (P<0.001). cTNI was also higher in the observation group (0.37±0.09 ng/mL vs 0.15±0.04 ng/mL, P<0.001). No statistical differences were found for other blood biochemical indicators, such as white blood cells, monocytes, neutrophils, lymphocytes, hemoglobin, platelets, PT, APTT, TT, fibrinogen, Cr and CRP.

Logistic regression analysis results

Multiple logistic regression analysis was performed on variables with a *P* value of <0.05 in the univariate analysis (LLDVT density ratio, D-dimer, Hcy, and cTNI), as shown in **Table 4**. Stepwise regression was used with the occurrence of PE as the dependent variable and the independent variables listed in **Table 5**. The results of the multiple logistic regression analysis, presented in **Table 6**, showed the following odds ratios (ORs) with 95% confidence intervals (CIs): LLDVT density ratio, 1.753 (1.247-4.169) (P<0.001); D-dimer, 1.402 (0.987-1.906) (P=0.058); Hcy, 1.945 (1.365-5.218) (P<0.001); and cTNI 1.536 (1.174-3.962) (P<0.001).

Comparison of risk factors (LLDVT density ratio, Wells scores, D-dimer, Hcy and cTNI) among groups with different risk levels

As shown in **Table 7**, the values of risk factors, including LLDVT density ratio, Wells scores, D-dimer, Hcy, and cTNI, were significantly lower in the low-risk group compared to the moderate

Table 2. The comparison of clinical characteristics between control group and observation group

Parameters	Control group (N=255)	Observation group (N=45)	t/χ^2	*P*
The location of lower extremity DVT			1.422	0.491
Proximal DVT	53 (20.78%)	7 (15.56%)		
Distal DVT	107 (41.96%)	23 (51.11%)		
Proximal and distal DVT	95 (37.26%)	15 (33.33%)		
The side of lower extremity DVT			2.523	0.283
Right side	89 (34.90%)	13 (28.89%)		
Left side	94 (36.86%)	14 (31.11%)		
Bilateral sides	72 (28.24%)	18 (40.00%)		
Lower limb deep vein thrombosis density ratio (%)	39.78±9.65	49.92±10.58	6.404	<0.001
Course of disease in tumor			1.924	0.382
<1 month	45 (17.65%)	9 (20.00%)		
1-6 months	130 (50.98%)	18 (40.00%)		
>6 months	80 (31.37%)	18 (40.00%)		
The type of malignant tumors			4.696	0.096
Lung cancer	80 (31.37%)	21 (46.67%)		
Gastrointestinal tumor	131 (51.37%)	20 (44.44%)		
Others	44 (17.25%)	4 (8.89%)		
The type of lung cancer			0.357	0.837
Adenocarcinoma	40 (50.00%)	11 (52.38%)		
Squamous carcinoma	24 (30.00%)	5 (23.81%)		
Small cell carcinoma	16 (20.00%)	5 (23.81%)		
The type of gastrointestinal tumor			0.456	0.500
Gastric carcinoma	68 (51.91%)	12 (60.00%)		
Colorectal cancer	63 (48.09%)	8 (40.00%)		
Caprini scores			1.594	0.451
0-2 scores	26 (10.20%)	2 (4.44%)		
2-4 scores	106 (41.57%)	21 (46.67%)		
>4 scores	123 (28.23%)	22 (48.89%)		
Long-term bedridden (>48 h)	18 (7.06%)	5 (11.11%)		
The implantation of PICC	85 (33.33%)	21 (46.67%)		
Treatment methods for DVT			1.046	0.903
Low molecular heparin	130 (50.98%)	25 (55.56%)		
Novel oral anticoagulant	28 (10.98%)	6 (13.33%)		
Early mobilization	16 (6.27%)	4 (8.89%)		
Others	12 (4.71%)	1 (2.22%)		
No precautionary measures	36 (14.12%)	8 (17.78%)		
Surgery in hospital	56 (21.96%)	11 (24.44%)	0.136	0.712
Chemotherapy	85 (33.33%)	18 (40.00%)	0.754	0.385
Radiotherapy	10 (3.92%)	2 (4.44%)	0.027	0.869
Targeted therapy	94 (36.86%)	23 (51.11%)	3.264	0.071
Immunological therapy	8 (3.14%)	3 (6.67%)	1.349	0.246
Tumor staging			1.991	0.158
I-II stages	51 (20.00%)	5 (11.11%)		
III-IV stages	204 (80.00%)	40 (88.89%)		
Wells scores	3.19±0.87	7.18±1.09	27.240	<0.001

Note: PICC: Peripherally inserted central catheter.

Table 3. The comparison of blood biochemical indicators between control group and observation group

Parameters	Control group (N=255)	Observation group (N=45)	t/χ^2	*P*
White blood cells ($\times10^9$/L)	6.35±1.62	6.17±1.43	0.699	0.485
Monocytes ($\times10^9$/L)	0.41±0.08	0.43±0.09	1.517	0.130
Neutrophils ($\times10^9$/L)	3.72±1.03	4.02±1.16	1.767	0.078
Lymphocytes ($\times10^9$/L)	1.00±0.42	0.98±0.37	0.300	0.765
Haemoglobin (g/L)	122.00±27.39	116.57±25.84	1.236	0.217
Blood platelet ($\times10^9$/L)	196.73±50.42	200.28±54.61	0.430	0.668
D-dimer (mg/L)	3.55±1.13	4.08±1.21	2.870	0.004
PT (s)	12.05±0.54	11.94±0.62	1.231	0.219
APTT (s)	29.54±1.63	30.03±1.52	1.877	0.061
TT (s)	15.28±2.35	15.03±1.98	0.673	0.502
Fibrinogen (g/L)	3.72±0.64	3.65±0.58	0.686	0.494
Cr (μmol/L)	79.74±16.28	83.72±17.91	1.489	0.138
CRP (mg/L)	28.45±6.71	30.28±8.92	1.599	0.111
Hcy (μmol/L)	10.38±2.06	26.42±2.53	46.440	<0.001
cTNI (ng/mL)	0.15±0.04	0.37±0.09	26.890	<0.001
PLR	187.84±32.56	170.84±28.56	1.546	0.123
SII	715.62±68.73	697.48±59.46	1.664	0.097
NLR	3.74±0.75	3.56±0.61	1.523	0.129

Note: PT: Prothrombin time; APTT: Activated partial thromboplastin time; TT: Thrombin time; Cr: Creatinine; CRP: C-reactive protein; Hcy: Homocysteine; cTNI: Cardiac troponin I.

Table 4. A univariate logistic regression analysis for risk factors of PE in malignant tumors patients with lower extremity deep vein thrombosis

Parameters	OR (95% CI)	P
Lower limb deep vein thrombosis density ratio (%)	1.286 (1.095-3.247)	<0.001
Wells scores	2.184 (1.127-4.305)	<0.001
D-dimer (mg/L)	2.743 (1.011-6.948)	0.041
Hcy (μmol/L)	1.378 (1.108-2.915)	0.003
cTNI (ng/mL)	4.017 (1.296-11.958)	0.002

Table 5. The assignment of independent variable in multiple logistic regression analysis

Independent variable	Assignment	
	0	1
Lower limb deep vein thrombosis density ratio (%)	≤48.61	>48.61
Wells scores	≤6.95	>6.95
D-dimer (mg/L)	≤3.87	>3.87
Hcy (μmol/L)	≤23.58	>23.58
cTNI (ng/mL)	≤0.32	>0.32

and high-risk groups (all P<0.05). Additionally, the values in the moderate-risk group were significantly lower than those in the high-risk group, with statistical differences observed among the three groups (P<0.001).

Correlation of LLDVT density ratio, Hcy and cTNI with Wells scores

As shown in **Table 2**, the Wells scores in the observation group were significantly higher than those in the control group (7.18±1.09 vs 3.19±0.87, t=27.240, P<0.001). Additionally, as demonstrated in **Figure 3A-C**, Pearson correlation analysis revealed a positive association between the LLDVT density ratio, Hcy, and cTNI with Wells scores. The correlation coefficients were 0.822, 0.899, and 0.890, respectively (all P<0.001).

Table 6. Multiple logistic regression analysis for risk factors of PE in malignant tumors patients with lower extremity deep vein thrombosis

Parameters	β	SE	Wald	P	OR (95% CI)
Lower limb deep vein thrombosis density ratio (%)	0.385	0.114	11.503	<0.001	1.753 (1.247-4.169)
Wells scores	0.374	0.138	9.495	<0.001	1.891 (1.412-6.038)
D-dimer (mg/L)	0.465	0.214	3.765	0.058	1.402 (0.987-1.906)
Hcy (μmol/L)	0.502	0.149	10.394	<0.001	1.945 (1.365-5.218)
cTNI (ng/mL)	0.476	0.155	8.967	<0.001	1.536 (1.174-3.962)

Note: Hcy: Homocysteine; cTNI: Cardiac troponin I.

Table 7. The comparative results among different groups

Groups	Lower limb deep vein thrombosis density ratio (%)	Hcy (μmol/L)	cTNI (ng/mL)	Wells scores
Low risk (n=15)	43.90±3.95	20.07±2.14	0.27±0.03	6.52±0.77
Moderate risk (n=18)	50.72±4.38	27.14±2.56	0.39±0.08	7.03±0.98
High risk (n=12)	56.24±5.10	33.28±3.07	0.46±0.09	8.27±1.01
F value	26.151	88.670	25.371	12.412
P value	<0.001	<0.001	<0.001	<0.001

Note: Hcy: Homocysteine; cTNI: Cardiac troponin I.

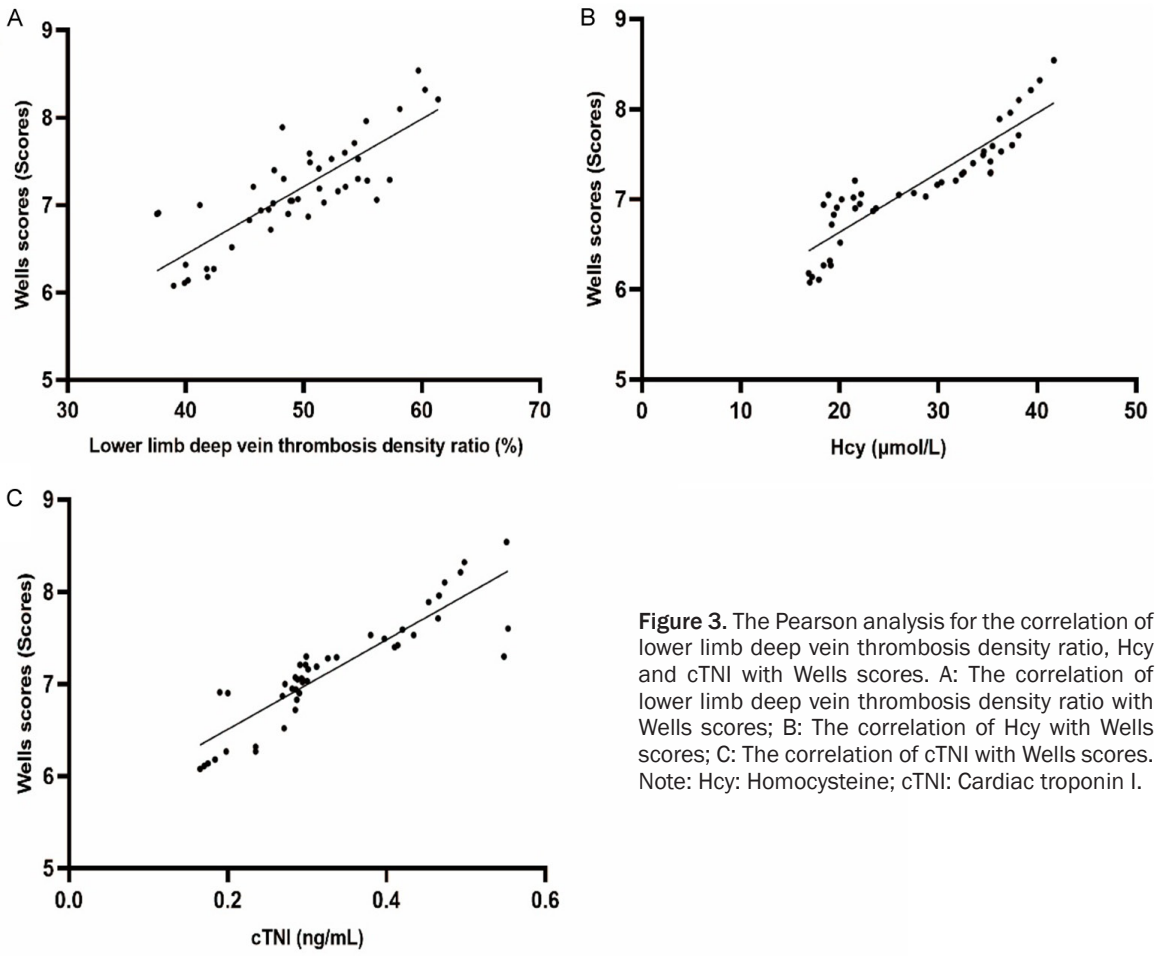

Figure 3. The Pearson analysis for the correlation of lower limb deep vein thrombosis density ratio, Hcy and cTNI with Wells scores. A: The correlation of lower limb deep vein thrombosis density ratio with Wells scores; B: The correlation of Hcy with Wells scores; C: The correlation of cTNI with Wells scores. Note: Hcy: Homocysteine; cTNI: Cardiac troponin I.

Table 8. The predictive value of lower limb deep vein thrombosis density ratio, Hcy and cTNI for diagnosing the occurrence of PE in malignant tumors patients with lower extremity deep vein thrombosis

Parameters	AUC	95% CI	*P* value	Cut-off value	Sensitivity (%)	Specificity (%)
Lower limb deep vein thrombosis density ratio (%)	0.714	0.481-0.913	0.004	48.61	73.33	65.88
Hcy (μmol/L)	0.736	0.394-0.898	0.013	23.58	75.56	62.75
cTNI (ng/mL)	0.762	0.417-0.924	0.008	0.32	77.78	69.80
The combined index	0.852	0.623-0.945	<0.001	-	86.67	90.20

Note: Hcy: Homocysteine; cTNI: Cardiac troponin I; AUC: Area under the curve.

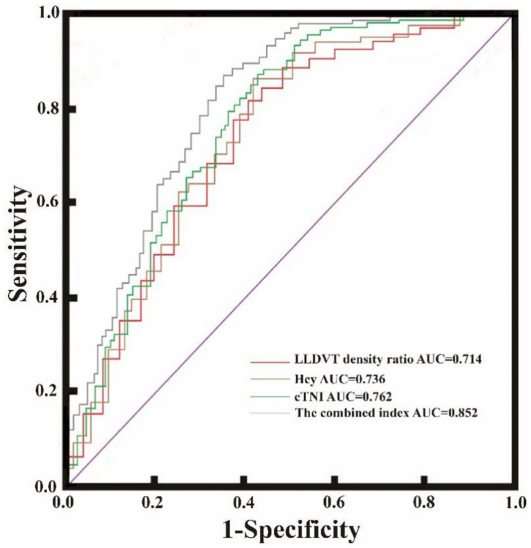

Figure 4. ROC curves evaluated the performance of lower limb deep vein thrombosis density ratio, Hcy and cTNI in diagnosing the occurrence of PE in malignant tumors patients with lower extremity deep vein thrombosis. Note: Hcy: Homocysteine; cTNI: Cardiac troponin I; AUC: Area under the curve; ROC: Relative operating characteristic.

Predictive value of LLDVT density ratio, Hcy, and cTNI for PE

As shown in **Table 8** and **Figure 4**, LL DVT density ratio, Hcy, and cTNI alone showed some predictive value for PE in malignant tumor patients with LLDVT. The area under the curve (AUC) for LLDVT density ratio, Hcy, and cTNI were 0.714, 0.736, and 0.762, respectively. The combined index had the highest predictive value, with an AUC of 0.852, and sensitivity and specificity values of 86.67% and 90.20%, respectively. Moreover, the comparison of AUCs using DeLong's test showed that the combined index had significantly greater diagnostic power than any individual risk factor, with statistically significant differences, as shown in **Table 9**.

Discussion

Despite advances in oncology and vascular medicine, cancer remains a common risk factor for the development of venous thromboembolism. Sakuma et al. found that malignant tumors not only induced thrombotic PE, but also caused tumor-related PE [20]. Numerous studies have shown that cancer patients have a four- to eight-fold higher risk of mortality after a thrombotic event compared to patients without malignancies [21]. It has also been documented that PE in cancer patients is associated with a poor prognosis [22]. As the signs and symptoms of PE are neither sensitive nor specific, diagnosing PE in cancer patients remains challenging. It has been noted that clinically unsuspected PE is often discovered only at autopsy [23]. Therefore, early identification of relevant risk factors for PE in these patients is crucial to facilitate clinical treatment. Currently, accurately predicting PE through a single biomarker remains difficult, and it is generally recommended to use multiple indicators for a combined examination to improve prediction accuracy [24].

The clinical characteristics of PE in cancer patients continue to be an area of interest. Previous studies have confirmed that patients with a history of trauma, surgery, chronic lung disease, high levels of D-dimer, SII, NLR and PLR are more prone to PE [25, 26]. In contrast, this study compared clinical data between the two groups and further evaluated the results using logistic regression analysis. The findings revealed that independent risk factors for predicting PE in cancer patients with LLDVT were the LLDVT density ratio, Hcy and cTNI, which differs from previous studies [27, 28]. This discrepancy may be due to differences in sample size and subject selection.

Table 9. The pairwise comparisons among the AUC of lower limb deep vein thrombosis density ratio, Hcy and cTNI and the jointed indexes

Comparisons of variables	Difference between areas (95% CI)	Z test	*P* value
LLDVT density ratio vs. Jointed indexes	0.321 (0.145-0.678)	6.032	<0.001
Hcy vs. Jointed indexes	0.279 (0.136-0.508)	6.244	<0.001
cTNI vs. Jointed indexes	0.175 (0.112-0.495)	4.879	<0.001

Note: LLDVT: Lower limb deep vein thrombosis; Hcy: Homocysteine; cTNI: Cardiac troponin I.

In clinical practice, the Wells score, a widely used clinical scoring system, is particularly applicable to the Chinese population. The Wells score includes clinical presentation, laboratory indicators, imaging examinations, and other factors. Multiple studies have confirmed that the Wells score effectively predicts the incidence of PE [29]. In this study, the Wells score in the observation group was significantly higher than in the control group, indicating that the Wells score could effectively predict PE in cancer patients with DVT, which aligns with the findings of Zaleski et al. [30].

Previous studies have shown that D-dimer levels effectively predict PE in patients with DVT. The fibrinolytic system is activated following thrombus formation, leading to the degradation of cross-linked fibrin into soluble degradation products, such as D-dimer, which reflect the body's hypercoagulable state and secondary fibrinolytic activity. Elevated D-dimer levels may be associated with concurrent LLDVT and pulmonary artery thrombosis, triggering a stronger fibrinolytic response in the body [31]. In this study, significant differences in D-dimer levels were observed between the two groups. Univariate logistic regression analysis also indicated that D-dimer was a risk factor for predicting PE in cancer patients with LLDVT. However, this effect was not significant in multivariate logistic regression analysis. The possible reason may be associated with the sample size or the selected subjects. And these inconsistencies in findings demanded more research to be complemented.

The thrombus density ratio is determined by measuring the CT Hounsfield units (HU) of the thrombus, which helps identify its composition and reflects the sharpness of blood clots and the concentration of red blood cells. Many studies have shown that thrombi with higher density ratios contain a significant amount of red blood cells rich in hemoglobin, as well as some fibrin. These thrombi are more sensitive to fibrinolytic agents, leading to poorer stability and a greater tendency to detach [32, 33]. Another study revealed that white thrombi, rich in platelet fragments, had lower CT HU values and greater resistance to fibrinolysis compared to red blood cell-rich thrombi [34]. In this study, it was found that the LLDVT density ratio in cancer patients with DVT and PE was higher than that in patients with DVT alone, which aligns with the findings of Yu et al. [35]. Additionally, the results indicated that PE patients with higher erythrocyte counts and lower platelet counts had higher CT HU values compared to those with DVT alone. The risk of PE decreased as platelet count increased.

cTnI is exclusively present in myocardial cells. When myocardial damage occurs under various conditions, cTnI levels rise rapidly within 4-6 hours and remain elevated for 6-10 days. In cases of PE in DVT patients, the sudden increase in pulmonary pressure leads to right ventricular strain, followed by right ventricular dilation, increased myocardial tension, and even compression of the coronary arteries. This impairs coronary artery perfusion, resulting in myocardial hypoxia, ischemia, and microinfarction, ultimately leading to elevated cTnI levels [36]. Another study found that elevated cTnI levels were associated with an increased short-term mortality risk related to PE [37]. As a marker for right ventricular injury and large thrombus burden, cTnI is also linked to higher long-term mortality risk due to PE [38]. Furthermore, the American Heart Association's guidelines for managing massive and submassive PE categorize patients with elevated cTnI as having submassive PE [39]. In this study, cTnI levels were higher in the observation group compared to the control group, suggesting that cTnI could be used to predict PE in cancer patients with DVT.

Hcy is an intermediate metabolite of sulfur-containing amino acids and a known risk factor for atherosclerosis. Hcy can cause endothelial cell damage, reduce vascular elasticity, and impair the coagulation process. Additionally, elevated Hcy levels can enhance platelet and endothelial cell adhesion, contributing to the formation of thrombogenic precursors [40, 41]. It has been suggested that Hcy promotes thrombus formation, confirming its association with an increased risk of venous thrombosis, making it an independent risk factor for thromboembolic diseases. One study reported that for every 1 μmol/L increase in Hcy, the risk of PE increased by approximately 10% [42]. The results of this study showed that Hcy levels in cancer patients with DVT and PE were higher than those in cancer patients with DVT alone. High levels of Hcy can damage endothelial cells, disrupt platelet arachidonic acid metabolism, promote thromboxane A2 synthesis, and activate the extrinsic coagulation pathway, stimulating platelets and inhibiting protein C and other coagulation factors. This creates a hypercoagulable state, increasing the risk of PE [43]. This mechanism likely explains why elevated Hcy levels correlate with a higher risk of PE in our analysis.

This study also found that the values of LLDVT density ratio, Hcy, cTnI, and Wells scores were highest in the high-risk group and lowest in the low-risk group among the three groups. Moreover, Pearson correlation analysis showed that the LLDVT density ratio, Hcy, and cTnI were positively associated with Wells scores. These results provide a reference for clinical risk stratification and the determination of treatment strategies for PE patients with cancer and DVT. Some studies have suggested that combining multiple PE risk assessment models improves the accuracy of PE screening [44]. Another study showed that a combination of biomarkers could effectively stratify and predict PE risk in cancer patients [45]. In this study, ROC curve analysis showed that the area under the curve for the combined LLDVT density ratio, Hcy, and cTnI was significantly higher than for any individual factor, indicating that the combined model had better predictive ability for PE. This model had a sensitivity of 86.67% and a specificity of 90.20% in predicting PE in cancer patients with DVT.

In conclusion, the LLDVT density ratio, Hcy, and cTnI were identified as independent risk factors for PE in cancer patients with lower extremity DVT. The diagnostic specificity increased with the number of risk factors. The combined detection of these indicators showed a sensitivity of 86.67% and specificity of 90.20% in predicting PE, making it a useful tool for evaluating PE occurrence in cancer patients with LLDVT. This combined approach should be promoted and applied in clinical practice, as it can improve patient management and prognosis. These findings suggest that clinicians should be more vigilant regarding the occurrence of PE in cancer patients with LLDVT. According to current guidelines, indefinite or extended anticoagulation should be considered for these patients with persistent risk factors. The duration of anticoagulation should be adjusted based on the patient's risk profile, balancing bleeding risks and the need for anticoagulant therapy.

However, this study has some limitations. It is a single-center study without long-term follow-up, and the sample size is relatively small. Additionally, the study lacked randomization, which could have led to observational bias. The underlying mechanisms were not explored in detail. Future research should include multicenter, large sample, randomized controlled trials with long-term follow-up to confirm these findings.

Disclosure of conflict of interest

None.

Address correspondence to: Hui Zheng, Department of Vascular Surgery, General Surgery Clinical Center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, No. 100, Haining Road, Shanghai 200080, China. Tel: +86-021-63240090; Fax: +86-021-63240090; E-mail: huizheng_@hotmail.com; Yuan Gao, Department of Vascular Surgery, The Second Affiliated Hospital of Shandong First Medical University, No. 366, Taishan Avenue, Tai'an 271000, Shandong, China. Tel: +86-0538-6236901; Fax: +86-0538-6236901; E-mail: xtyygaoyuan@163.com

References

[1] de Wit K and D'Arsigny CL. Risk stratification of acute pulmonary embolism. J Thromb Haemost 2023; 21: 3016-3023.
[2] Barca-Hernando M, Lopez-Ruz S, Marin-Romero S, Elias-Hernandez T, Otero-Candelera R and

Jara-Palomares L. Comparison of long-term complications in cancer patients with incidental and acute symptomatic venous thromboembolism. Front Cardiovasc Med 2023; 10: 1118385.
[3] Tirandi A, Preda A, Carbone F, Montecucco F and Liberale L. Pulmonary embolism in patients with cancer: an updated and operative guide for diagnosis and management. Int J Cardiol 2022; 358: 95-102.
[4] Donnellan E, Kevane B, Bird BR and Ainle FN. Cancer and venous thromboembolic disease: from molecular mechanisms to clinical management. Curr Oncol 2014; 21: 134-143.
[5] Au C, Gupta E, Khaing P, Dibello J, Chengsupanimit T, Mitchell EP, West FM, Baram M, Awsare BK and Kane GC. Clinical presentations and outcomes in pulmonary embolism patients with cancer. J Thromb Thrombolysis 2021; 51: 430-436.
[6] Meignan M, Rosso J, Gauthier H, Brunengo F, Claudel S, Sagnard L, d'Azemar P, Simonneau G and Charbonnier B. Systematic lung scans reveal a high frequency of silent pulmonary embolism in patients with proximal deep venous thrombosis. Arch Intern Med 2000; 160: 159-164.
[7] Xue X and Sista AK. Catheter-directed thrombolysis for pulmonary embolism: the state of practice. Tech Vasc Interv Radiol 2018; 21: 78-84.
[8] Glise Sandblad K, Rosengren A, Sorbo J, Jern S and Hansson PO. Pulmonary embolism and deep vein thrombosis-comorbidities and temporary provoking factors in a register-based study of 1.48 million people. Res Pract Thromb Haemost 2022; 6: e12714.
[9] Nagel SN, Steffen IG, Schwartz S, Hamm B and Elgeti T. Age-dependent diagnostic accuracy of clinical scoring systems and D-dimer levels in the diagnosis of pulmonary embolism with computed tomography pulmonary angiography (CTPA). Eur Radiol 2019; 29: 4563-4571.
[10] Verso M, Franco L, Giustozzi M, Becattini C and Agnelli G. Treatment of venous thromboembolism in patients with cancer: what news from clinical trials? Thromb Res 2018; 164 Suppl 1: S168-S171.
[11] Jara-Palomares L, van Es N, Praena-Fernandez JM, Le Gal G, Otten HM, Robin P, Piccioli A, Lecumberri R, Religa P, Rieu V, Rondina M, Beckers M, Prandoni P, Salaun PY, Di Nisio M, Bossuyt PM, Kraaijpoel N, Buller HR and Carrier M. Relationship between type of unprovoked venous thromboembolism and cancer location: an individual patient data meta-analysis. Thromb Res 2019; 176: 79-84.
[12] Aggarwal A, Fullam L, Brownstein AP, Maynard GA, Ansell J, Varga EA, Friedman RJ and Rickles FR. Deep vein thrombosis (DVT) and pulmonary embolism (PE): awareness and prophylaxis practices reported by patients with cancer. Cancer Invest 2015; 33: 405-410.
[13] Khandait H, Harkut P, Khandait V and Bang V. Acute pulmonary embolism: diagnosis and management. Indian Heart J 2023; 75: 335-342.
[14] Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jimenez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ainle FN, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E and Zamorano JL; The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019; 54: 1901647.
[15] Linnemann B, Beyer-Westendorf J, Espinola-Klein C, Muhlberg KS, Muller OJ and Klamroth R. Management of deep vein thrombosis: an update based on the revised AWMF S2k guideline. Hamostaseologie 2024; 44: 97-110.
[16] Essien EO, Rali P and Mathai SC. Pulmonary embolism. Med Clin North Am 2019; 103: 549-564.
[17] Wang RH, Wen WX, Jiang ZP, Du ZP, Ma ZH, Lu AL, Li HP, Yuan F, Wu SB, Guo JW, Cai YF, Huang Y, Wang LX and Lu HJ. The clinical value of neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and systemic inflammation response index (SIRI) for predicting the occurrence and severity of pneumonia in patients with intracerebral hemorrhage. Front Immunol 2023; 14: 1115031.
[18] Dempfle CE, Korte W, Schwab M, Zerback R and Huisman MV; CARDIM study group. Sensitivity and specificity of a quantitative point of care D-dimer assay using heparinized whole blood, in patients with clinically suspected deep vein thrombosis. Thromb Haemost 2006; 96: 79-83.
[19] Liu W, Song S, Zhang H and An C. A comparative analysis of anthropometric indices for diagnosing obstructive sleep apnea among American adults. Sci Rep 2024; 14: 29578.
[20] Sakuma M, Fukui S, Nakamura M, Takahashi T, Kitamukai O, Yazu T, Yamada N, Ota M, Kobayashi T, Nakano T and Shirato K. Cancer and pulmonary embolism: thrombotic embolism,

tumor embolism, and tumor invasion into a large vein. Circ J 2006; 70: 744-749.
[21] Fuentes HE, Tafur AJ, Caprini JA, Alatri A, Trujillo-Santos J, Farge-Bancel D, Rosa V, Font L, Vilaseca A and Monreal M; RIETE Investigators. Prediction of early mortality in patients with cancer-associated thrombosis in the RIETE database. Int Angiol 2019; 38: 173-184.
[22] Zuin M, Nohria A, Henkin S, Krishnathasan D, Sato A and Piazza G. Pulmonary embolism-related mortality in patients with cancer. JAMA Netw Open 2025; 8: e2460315.
[23] Stein PD and Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest 1995; 108: 978-981.
[24] Cui YQ, Tan XM, Liu B, Zheng Y, Zhang LY, Chen ZA and Wu XL. Analysis on risk factors of lung cancer complicated with pulmonary embolism. Clin Respir J 2021; 15: 65-73.
[25] Siddiqui F, Tafur A, Hussain M, Garcia-Ortega A, Darki A, Fareed J, Jimenez D, Bikdeli B, Galeano-Valle F, Fernandez-Reyes JL, Perez-Pinar M and Monreal M; RIETE Investigators. The prognostic value of blood cellular indices in pulmonary embolism. Am J Hematol 2024; 99: 1704-1711.
[26] Becattini C and Agnelli G. Risk stratification and management of acute pulmonary embolism. Hematology Am Soc Hematol Educ Program 2016; 2016: 404-412.
[27] Soo Hoo GW. Overview and assessment of risk factors for pulmonary embolism. Expert Rev Respir Med 2013; 7: 171-191.
[28] Chowdhury JM, Brown P and Kasarabada A. Risk stratification of pulmonary embolism. Curr Opin Pulm Med 2023; 29: 363-369.
[29] Shen JH, Chen HL, Chen JR, Xing JL, Gu P and Zhu BF. Comparison of the wells score with the revised Geneva score for assessing suspected pulmonary embolism: a systematic review and meta-analysis. J Thromb Thrombolysis 2016; 41: 482-492.
[30] Zaleski AL, Taylor BA, Pescatello LS, Thompson PD and Denegar C. Performance of wells score to predict deep vein thrombosis and pulmonary embolism in endurance athletes. Phys Sportsmed 2017; 45: 358-364.
[31] Michiels JJ, Gadisseur A, van der Planken M, Schroyens W, De Maeseneer M, Hermsen JT, Trienekens PH, Hoogsteden H and Pattynama PM. Screening for deep vein thrombosis and pulmonary embolism in outpatients with suspected DVT or PE by the sequential use of clinical score: a sensitive quantitative D-dimer test and noninvasive diagnostic tools. Semin Vasc Med 2005; 5: 351-364.
[32] Yao MM, Lin TT, Shi X, Chen MG, Wu JX, Zhao YP and Lin BS. Thrombosis density ratio can predict the occurrence of pulmonary embolism and post-thrombotic syndrome in lower-extremity deep vein thrombosis patients. Clin Hemorheol Microcirc 2024; 86: 395-405.
[33] Jeong MJ, Kwon H, Noh M, Ko GY, Gwon DI, Lee JS, Kim MJ, Choi JY, Han Y, Kwon TW and Cho YP. Relationship of Lower-extremity deep venous thrombosis density at CT venography to acute pulmonary embolism and the risk of postthrombotic syndrome. Radiology 2019; 293: 687-694.
[34] Hasenberg U, Paul T, Feuersenger A, Goyen M and Kroger K. Cancer patients and characteristics of pulmonary embolism. Eur J Radiol 2009; 69: 478-482.
[35] Yu MH, Jung JH, Kim T and Kim DK. Thrombus volume and Hounsfield unit density as a predictor of pulmonary embolism in patients with deep vein thrombosis. Acta Radiol 2023; 64: 2198-2204.
[36] Caliskan T, Turkoglu O, Canoglu K, Ayten O, Saylan B, Okutan O and Kartaloglu Z. The comparison between non-high risk patients with and without cancer diagnosed with pulmonary embolism. Medeni Med J 2021; 36: 30-35.
[37] Becattini C, Vedovati MC and Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007; 116: 427-433.
[38] Janata KM, Leitner JM, Holzer-Richling N, Janata A, Laggner AN and Jilma B. Troponin T predicts in-hospital and 1-year mortality in patients with pulmonary embolism. Eur Respir J 2009; 34: 1357-1363.
[39] Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ and Zierler BK; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011; 123: 1788-1830.
[40] Gueant JL, Gueant-Rodriguez RM, Oussalah A, Zuily S and Rosenberg I. Hyperhomocysteinemia in cardiovascular diseases: revisiting observational studies and clinical trials. Thromb Haemost 2023; 123: 270-282.
[41] Faeh D, Chiolero A and Paccaud F. Homocysteine as a risk factor for cardiovascular disease: should we (still) worry about? Swiss Med Wkly 2006; 136: 745-756.

[42] Adam SK, Soelaiman IN, Umar NA, Mokhtar N, Mohamed N and Jaarin K. Effects of repeatedly heated palm oil on serum lipid profile, lipid peroxidation and homocysteine levels in a post-menopausal rat model. Mcgill J Med 2008; 11: 145-151.

[43] Herrmann M, Whiting MJ, Veillard AS, Ehnholm C, Sullivan DR and Keech AC; FIELD study investigators. Plasma homocysteine and the risk of venous thromboembolism: insights from the FIELD study. Clin Chem Lab Med 2012; 50: 2213-2219.

[44] Maraziti G, Cimini LA and Becattini C. Risk stratification to optimize the management of acute pulmonary embolism. Expert Rev Cardiovasc Ther 2022; 20: 377-387.

[45] Li Y, Liu Z, Chen C, Li D, Peng H, Zhao P and Wang J. Risk factors and potential predictors of pulmonary embolism in cancer patients undergoing thoracic and abdominopelvic surgery: a case control study. Thromb J 2022; 20: 80.