

Original Article

Long-term prognosis and related factors towards patients with acute pulmonary thromboembolism

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Abstract: This study aims to investigate the long-term prognosis and the affecting factors towards the patients with acute pulmonary thromboembolism (APTE). The clinical data of 903 PTE patients, diagnosed by the spiral CT pulmonary angiography (CTPA) or lung ventilation perfusion scanning when hospitalized in the Second Hospital of Hebei Medical University from January 1998 to December 2013, were collected, among who 548 patients were performed the long-term follow-up, and the factors that would affect the prognosis were statistically analyzed. The univariate analysis showed that many factors would affect the prognosis of PTE. The multivariate non-conditional logistic regression analysis showed that: the relevant factors of re-embolization included the idiopathic pulmonary embolism, RVD, D-dimer positive, anticoagulation treatment < 3 months, post-treatment PASP > 40 mmHg, the relevant factors of death included the D-dimer positive, anticoagulation treatment < 3 months, cTnl positive, post-treatment PASP > 40 mmHg. RVD and post-treatment PASP > 40 mmHg would increase the risk of chronic thromboembolic pulmonary hypertension (CTEPH). The idiopathic pulmonary embolism, RVD, D-dimer positive, anticoagulation treatment < 3 months, cTnl positive and post-treatment PASP > 40 mmHg were the important factors that would affect the long-term prognosis of PTE patients.

Keywords: Pulmonary thromboembolism, prognosis, risk factors

Introduction

The pulmonary thromboembolism (PTE) referred to a series of clinical and pathophysiological syndromes that were caused by the thrombosis of pulmonary artery or other branches, as a common emergency of internal medicine, its poor prognosis included the re-embolism, death, CTEPH and so on. With the development of medical technologies, its prognosis had become the focus of many scholars. Despite adequate treatment, up to one quarter of patients with symptomatic deep vein thrombosis (DVT) and/or pulmonary embolism (PTE) will experience recurrent venous thromboembolism (VTE) within the subsequent 5 years [1-3]. Of note, 25% of the patients do not survive the first year after diagnosis, although the majority of deaths during this time are related to underlying conditions such as cancer or chronic heart disease rather than to PE itself [4, 5]. Previous studies 1, 3 have reported an incidence of CTPH between 0.1% and 3.8% in patients with

previous venous thromboembolism (VTE) [6-8]. Currently, many researchers had found that the re-embolism rate of idiopathic PTE patients was more than 2-fold of non-idiopathic patients, especially the patients with temporary risk factors [1, 9, 10]. In addition, many scholars believed that the right ventricular dysfunction was the important cause of death towards the PTE patients, Zhu et al [11] found that the 14-day mortality of PTE patients associated with right ventricular dysfunction was significantly increased than those with normal right ventricular function (2.0% vs 0.4%, $P < 0.01$). Furthermore, the foreign studies had shown that the incidence of CTEPH was 0.5%-3.8% [6, 7, 12-14], and most CTEPH patients exhibited poor quality of life and prognosis. Therefore, it would be important to make clear the long-term prognosis and related factors of PTE patients.

Here we report on the prospective long-term follow-up of a large series of patients with PTE. All of them received conventional anticoagula-

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tion and/or thrombolytic therapy, and were then followed-up for a maximum of 12 years after the PTE was diagnosed in order to document the incidence of recurrent PTE, death and CTEPH, and analysis the risk factors.

Materials and methods

Case selection

The PTE patients, diagnosed by the spiral CT pulmonary angiography (CTPA) or lung ventilation perfusion scanning when hospitalized in the Second Hospital of Hebei Medical University from January 1998 to December 2013, were selected. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hebei Medical University. Written informed consent was obtained from all participants.

Inclusion criteria: 1. Based on the diagnostic criteria of "diagnosis and treatment guidelines of pulmonary thromboembolism", issued by the Respiratory Branch of Chinese Society in 2001 [15]. 2. with the disease duration less than two weeks. 3. According to the ESC PTE Guidelines in 2008, the high-risk group was performed the thrombolytic therapy, the middle-risk group was performed the thrombolytic or anticoagulant therapy based on the clinical circumstances and wishes of patients, and the low-risk group was performed the anticoagulant therapy. The oral anticoagulant therapy used the low molecular weight heparin and started within 1 week, and the anticoagulant treatment should be determined according to the real situations.

Clinical data collection

Patient-related information was screened, including communication information, general situation when admission, clinical manifestations, laboratory examinations, treatment methods, complications, re-embolism and death, etc.

Diagnosis of right heart dysfunction

RVD could be diagnosed when the patient met any one of the following conditions: 1. the right ventricle enlarged (diastolic trans diameter of right ventricle/diastolic trans diameter of left ventricle > 1, or diastolic anteroposterior diameter of right ventricle/diastolic anteroposterior diameter of left ventricle > 0.5, or end-diastolic

inner diameter of right ventricle > 25 mm); 2. the right ventricular wall motion weakened (amplitude of right ventricular anterior wall motion < 5 mm); 3. pressure overload (pulmonary artery systolic pressure > 30 mmHg).

Follow-up

The 3-month to 12-year follow-up was performed by telephone and patient's hospital visiting, and such necessary relevant checks as CTPA, UCG, lower limb-venous ultrasound, D-dimer, oral anticoagulation therapy were performed, with the focus as events and related factors of re-embolism, death and CTEPH, etc.

Statistical methods

The statistical analysis was performed by SPSS13.0 software package. The measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm s$), the intergroup comparison used the *t* test. The counting data were expressed as rate or construction proportion, the intergroup comparison used the χ^2 test (with $P < 0.05$ considered as the statistical significance). The multivariate analysis used the multivariate non-conditional logistic regression analysis to calculate the relative risk (RR) and confidence intervals (95% CI), with $P < 0.1$ considered as statistically significant.

Results

Patients

The clinical data of 903 PTE patients, diagnosed by the spiral CT pulmonary angiography (CTPA) or lung ventilation perfusion scanning when hospitalized in the Second Hospital of Hebei Medical University from January 1998 to December 2013, were collected. Among who 548 cases exhibited better compliance, the follow-up period was (2.34 \pm 1.20) years. Among the 548 follow-up cases, 66 cases died (12.04%), 48 cases exhibited the re-embolism (8.76%), and 20 cases exhibited the CTEPH (3.65%).

Basic features

520 cases were diagnosed by the pulmonary artery angiography (94.72%), 29 cases were diagnosed by the pulmonary ventilation perfusion scanning (5.28%), among who 270 cases were males and 278 cases were females, aged

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19 to 90 years old, with the mean age as (59.87±15.26) years old. The population aged over 40 years old, when PTE onset, accounted for 88.34%, while those under 40 years old accounted for 11.66%. Among the 48 cases of re-embolism, 23 were males and 25 were females, with the mean age as (57.66±13.57) years old, among the 66 cases of death, 41 cases were males and 25 cases were females, with the mean age as (65.22±13.05) years old, among 20 cases of CTEPH, 12 cases were males and 8 cases were females, with the mean age as (55.28±13.68) years old, among the 414 cases that did not occur the poor prognosis, 223 cases were males and 197 cases were females, with the average age as (58.93±15.69) years old, there was no statistical significance in the constituent ratios of sex and age among the four groups ($P > 0.05$).

Underlying diseases: The hypertension was the most common, accounting for 41.06% (225 cases), followed by 148 cases of DVT and (or) varicose vein of lower limbs (26.96%), 128 cases of long-term bed laying (23.32%), 97 cases of coronary heart disease (17.67%), 64 cases of diabetes (11.66%), 65 cases of chronic lung disease (11.84%), 135 cases of idiopathic patients (24.64%), 33 cases of trauma surgery (6.01%), 42 cases of heart failure (7.66%) and 16 cases of cancer (2.91%).

Clinical symptoms: The shortness of breath and breathing difficulty were the most common, accounting for 69.03% (379 cases), followed by 137 cases of chest pain (36.07%), 115 cases of syncope (20.95%). The occurrence rate of typical triad (dyspnea, chest pain and hemoptysis) was 4.56%. The signs of faster respiratory rate (291 cases, 53.01%), lower extremity edema or varicose veins (214 cases, 38.98%) and P2 hyperthyroidism (205 cases, 37.34%) were common.

Auxiliary examinations

All the patients were performed the electrocardiography, echocardiography, venous ultrasound examination and serological examination, among who 234 cases (42.62%) exhibited the ECG changes, including newly-emerged QRS right axis bias, SIQIII TIII, complete or incomplete bundle branch block, and inversion of pulmonary P wave and T wave. 450 patients (81.97%) were performed the echocardiography examination, and 208 cases exhibited

the right ventricular dilatation (46.22%), 174 cases exhibited the pulmonary hypertension (38.67%), with the mean pulmonary artery pressure as 58.72±23.10 mmHg, 42 patients exhibited the intracardiac thrombus (9.33%). 318 cases were performed the venous ultrasonography, and it was found that 201 cases had the deep vein thrombosis (63.21%). The serological examinations: 348 cases were performed the D-dimer examination, with the positive rate as 74.59%, and 237 cases were performed the clear troponin (cTnI) examination, with the positive rate as 11.45%. 489 cases were performed the arterial blood gas analysis, with the average arterial oxygen pressure as 76.49±22.81 mmHg, and the occurrence rate of hypoxemia was 19.02% (93 cases).

Prognosis: 548 patients were followed up for a period of 3 months to 12 years, during the follow-up period, 48 patients occurred the re-embolism, 5 patients occurred the chronic thromboembolic pulmonary hypertension, 66 patients died, including 19 PTE-related cases, 2 cases died of the blood diseases, 2 cases of malignant tumors, 8 cases of heart failure or respiratory failure, and another 35 cases had unknown or uncertain reasons.

During the hospitalization, 95 patients were performed the thrombolytic therapy, 2 cases were implanted the inferior vena cava filter, and only 3 cases exhibited serious gastrointestinal bleeding. 11 cases (2.00%) died during the hospitalization, among who 6 patients died of PTE, among the rest 5 cases, 3 cases died of malignant cancers, and 2 cases died of chronic lung disease-caused respiratory failure.

During January 2005 and December 2013, the annual incidence rates of PTE patients' death, re-embolism and CTEPH were decreased significantly, which were from 25.0%, 12.5% and 5.0% to 1.69%, 2.81% and 0.90%, respectively, thus it could be seen that the PTE diagnosis and treatment obtained the rapid progress in the recent years (**Figure 1**).

Analysis of relevant factors

The univariate analysis showed that: idiopathic PTE, DVT, heart failure, long-term bed laying, right ventricular dysfunction (RVD), D-dimer (D-dimer) positive, cTnI positive, anticoagulation treatment < 3 months, age > 65 years and post-treatment PASP > 40 mmHg were the risk

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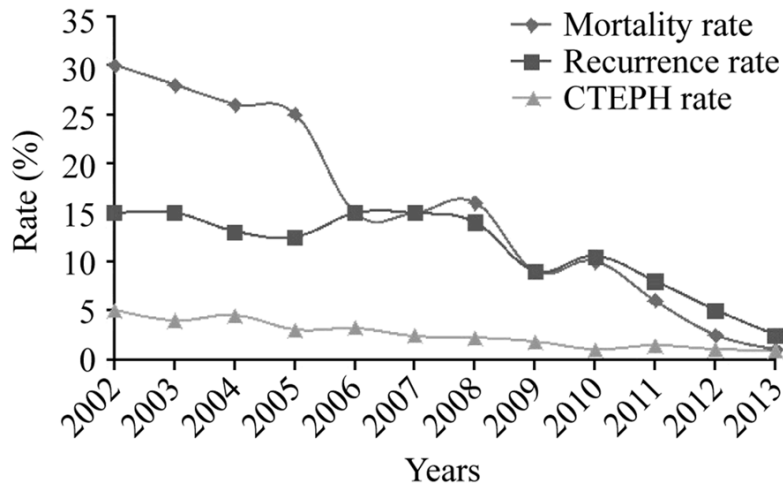


Figure 1. Trends of annual incidence rates of re-embolism, death and CTEPH in the acute PTE patients.

factors of re-embolism; deep vein thrombosis (DVT), chronic lung disease, heart failure, history of stroke, anticoagulation treatment < 3 months, thrombolytic treatment, long-term bed laying, hyperlipidemia, RVD, D-dimer positive, cTnI positive and post-treatment PASP > 40 mmHg were the a risk factors of death; idiopathic PTE, DVT, heart failure, coronary artery disease, hyperlipidemia, thrombolytic therapy, RVD, D-dimer positive, cTnI positive, hypoxemia, pre-treatment PASP > 50 mmHg and post-treatment PASP > 40 mmHg were the risk factors of CTEPH ($P < 0.05$, **Table 1**).

Multivariate unconditional logistic regression analysis

The multivariate unconditional logistic regression analysis revealed that the idiopathic PTE, RVD, D-dimer positive, anticoagulation treatment < 3 months and post-treatment PASP > 40 mmHg were associated with the re-embolism; D-dimer positive, anticoagulation treatment < 3 months, cTnI positive and post-treatment PASP > 40 mmHg were related with death; RVD and post-treatment PASP > 40 mmHg could increase the risk of CTEPH ($P < 0.05$, **Table 2**).

Discussion

The recent studies found that the incidence rate of re-embolism 3 months, 1 year, 3 years, 5 years and 10 years after the acute pulmonary embolism (APTE) were 5.7%, 11.0%, 19.6%,

29.1% and 39.9%, respectively, and the relative risk factors included idiopathic PE, aging, thrombophilia, primary DVT and too short anticoagulation treatment, etc. [16, 17]. The 30-day, 1-year and 3-year mortality were 13.0%, 26.0% and 35.3%, respectively, and the main related factors were instable hemodynamics, RVD and cTnI positive, etc. [18]. The CTEPH incidence rates 6 months, 1 year and 2 years after APTE were 1.0%, 3.1% and 3.8%, and mainly related with small onset age, persistent pulmonary thromboembo-

lism and idiopathic PTE, etc. [7]. This study performed the follow-up research towards the PTE patients within the recent 15 years, aiming to understand the prognosis-related factors of PTE, then minimize the mortality and morbidity. The results showed the idiopathic PTE, RVD, D-dimer positive, anticoagulation treatment < 3 months, cTnI positive and post-treatment PASP > 40 mmHg were the important factors that would affect the long-term prognosis of PTE patients.

Among the patients reported by Meneveau *et al.* [19], age > 75 years old, malignancy and post-thrombolysis persistent pulmonary obstruction > 30% were the major factors that would cause death. The short-term all-cause mortality of patients with echocardiographic RVD was 10%, while that of the patients without short-term echocardiographic RVD was 3%, the mortality of patients with RVD was significantly increased [20]. The retrospective study revealed that the right ventricular dilation in CT might be the independent predictor of all-cause mortality and adverse events of PTE patients [21]. The Meta-analysis of two retrospective studies showed that 47% PE patients exhibited the right ventricular dilation in CT, this study set the end-diastolic diameter ratio of right/left ventricle > 0.9 to 1.5 as the right ventricular dilation criteria. The short-term all-cause mortalities of the patients with or without right ventricular dilation were 14% and 6%. The risk increase of mortality of the patients with right ventricular dilation was not statistically signifi-

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Table 1. Single factor χ^2 test that would affect the long-term prognosis

Risk factor	Better prognosis 414 cases (%)	Re-embolism 48 cases (%)	χ^2	P	Death 66 cases (%)	χ^2	P	CTEPH 20 cases (%)	χ^2	P
Idiopathic PTE	94/414	38/48	67.189	0.000	17/66	0.298	0.342	16/20	33.099	0.000
Hypertension	190/414	28/48	3.172	0.052	25/66	1.479	0.319	8/20	0.267	0.390
DVT	117/396	21/40	5.700	0.017	22/59	7.839	0.005	12/20	8.254	0.006
CPD	53/414	3/48	1.733	0.137	17/66	7.670	0.007	4/20	0.866	0.261
HF	23/414	12/48	23.226	0.000	10/66	8.187	0.008	8/20	34.126	0.000
CHD	72/414	12/48	1.674	0.137	9/66	0.572	0.288	8/20	6.486	0.018
DM	52/414	3/48	1.633	0.147	10/66	0.340	0.339	0	2.854	0.073
Stroke	24/414	3/48	0.016	0.548	9/66	5.464	0.026	0	1.227	0.312
Thrombolysis	109/414	12/48	0.039	0.499	6/66	4.946	0.016	0	7.032	0.003
Surgery/trauma	24/414	3/48	0.016	0.548	4/66	0.007	0.554	0	1.227	0.312
Long-term bed laying	102/414	5/48	4.488	0.016	4/66	11.417	0.000	0	6.441	0.004
Hyperlipidemia	17/414	1/48	0.470	0.424	19/66	49.986	0.000	8/20	45.279	0.000
Cancer	10/414	2/48	0.521	0.360	2/66	0.088	0.509	0	0.494	0.621
RVD	99/337	32/45	33.744	0.000	24/51	19.721	0.000	20/20	42.374	0.000
D-dimer positive	262/346	45/48	20.097	0.000	39/46	21.487	0.000	4/20	29.564	0.000
cTnI positive	11/260	8/40	18.913	0.000	5/30	5.772	0.016	4/20	9.108	0.016
Anticoagulation therapy < 3 m	42/414	10/48	4.920	0.031	12/66	3.683	0.049	4/20	1.955	0.151
Hypoxemia	64/414	5/48	0.861	0.244	6/66	1.853	0.117	8/20	8.304	0.009
Male	221/414	21/48	1.800	0.133	30/66	1.434	0.144	12/20	0.336	0.365
Age > 65	148/414	9/48	5.540	0.012	28/66	1.092	0.182	4/20	2.079	0.112
Pre-treatment PASP > 50	126/330	14/43	0.513	0.474	22/59	0.017	0.896	20/20	29.639	0.000
Post-treatment PASP > 40	11/58	13/24	10.161	0.001	14/42	36.592	0.000	16/20	24.995	0.000

Note: DVT: deep vein thrombosis; CPD: chronic pulmonary disease; HF: heart failure; CHD: coronary heart disease; DM: diabetes; RVD: Right ventricular dysfunction; PASP: pulmonary artery systolic pressure.

Table 2. Multivariate unconditional logistic regression analysis that would affect the long-term prognosis

	Risk factor	RR	95% CI	P
Re-embolism	RVD	8.05	2.85-22.78	0.000
	D-dimer positive	5.89	1.35-25.68	0.018
	Idiopathic PTE	20.09	5.85-69.02	0.000
	Post-treatment PASP > 40	10.39	3.49-30.90	0.000
	Anticoagulation therapy < 3 m	2.23	1.06-3.49	0.03
Death	D-dimer positive	3.83	1.01-14.53	0.049
	Post-treatment PASP > 40	7.20	1.62-31.97	0.009
	Anticoagulation therapy < 3 m	5.36	1.14-25.23	0.033
CTEPH	cTnI positive	7.04	1.39-35.66	0.018
	RVD	1.40	1.12-3.32	0.048
	Post-treatment PASP > 40	2.37	1.15-6.12	0.007

cant (RR = 2.3, 95 CI = 0.9-6.0) [20]. This study and the above literatures all suggested the existence of continued pulmonary vascular obstruction after the PTE treatment, especially the post-treatment PASP > 40 mmHg would result in the pulmonary hypertension and RVD; the right ventricular dilation would cause the septal left shifting, left ventricular dysfunction, followed by the cardiac output declining, which would thereby cause the systemic hypotension

or shock; the low intra-aortic blood pressure and high right atrial pressure would cause the gradient declining of coronary perfusion and myocardial blood flow, especially the right ventricular subendocardial cardiac muscle would be in the status of hypo-perfusion. At the same time, the nervous and humoral factors activated the sympathetic nervous system, resulting in the positive chronotropic and inotropic changes, meanwhile under the Frank-Starling mechanism, the cardiac output was increased

to maintain the stability of pulmonary circulation blood volume and systemic blood pressure. The combined effects of the above situations resulted in the increase of myocardial oxygen demand and gradient descent of coronary perfusion, which would lead to the myocardial injury, create a vicious cycle and affect the prognosis [22], so that the incidence rates of such adverse outcomes as re-embolism, death and CTEPH would increase.

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In addition, the idiopathic PTE was also an important factor that would affect the prognosis of patients. Due to the unknown reasons, it would often be difficult to perform the targeted prevention measures, so the majority of scholars agreed that the anticoagulant treatment of the patients with idiopathic PTE should be longer than six months, even lifelong. This study showed that the idiopathic PTE could increase patients' thrombosis and mortality, which might be related with the repeated embolization caused by the unknown difficult-to-prevent risk factors, low level attention from the patients and no adherence to the long-term anticoagulant therapy.

D-dimer positive was also an important factor that would affect the prognosis of PTE patients. Cosmi et al [23] found that in a case-control study that compared with the sustained negative patients, the re-embolism rate of continuous D-dimer positive (HR = 9.38) or turned positive within three months and continued positive was higher (HR = 3.78). Based on the D-dimer levels (immunoturbidimetric assay), Palareti et al. [24] divided the PTE patients into three layers (D-dimer 500-2499 ng/mL, 2500-4999 ng/mL and > 5000 ng/mL), the distribution of these 3 groups' patients were 47.8%, 26.0% and 20.4%; D-dimer 500-2499 ng/mL was set as the reference, the relative risks of death of the following two groups increased in turn (OR, 1.91 and 2.94 respectively), and the death risk of fatal pulmonary embolism in the D-dimer > 5000 ng/mL PTE patients was significantly higher than those combined with cancer, braking, renal dysfunction and other complications (OR = 4.4 vs 2.1). Through the univariate and multivariate analysis. This study also showed that the continuous D-dimer positive could increase the re-embolism and mortality rates of the PTE patients.

The inadequate anticoagulation treatment could also increase the incidence rate of adverse events in the PTE patients. Ageno et al [25] found that the standard anticoagulation intensity could reduce the risk of re-thrombosis than the low-intensity, while did not significantly increase the risk of bleeding. In addition, this study also found that the re-embolism rate towards the low international normalized ratio (INR) was higher than those with the standard intensity (1.9% vs 0.9%), and the longer the target-achieving time in the early INR treat-

ment, the higher the re-embolism rate at the end of anticoagulation [26]. In addition, the inadequate period or intensity of anticoagulation, post-treatment persistent thrombosis and general obstruction of pulmonary vascular bed more than 40% would form CTEPH and RVD [6], thus leading to the right heart failure, even the whole heart failure, which would reduce the patients' life quality, even increase the mortality. Furthermore, CTEPH exhibited the progressive development, and poor results towards the drug treatment, the effects of non-surgical treatment could not be entirely ensured. Through the long-term follow-up, this study found that the incidence rate of CTEPH was 3.88%, slightly higher than the above studies. Therefore, the prevention and effective treatment of CTEPH still needed the further study.

The recent studies had found that partial acute PTE patients also exhibited the elevated serum troponin levels, and significantly correlated with the short-term prognosis of patients. The Meta analysis of 20 studies showed that 31 PTE patients exhibited the elevated troponin levels. The determination of troponin and definition of abnormal value varied largely among different studies. The significantly increased troponin was also associated with the increased short-term all-cause mortality (OR = 52, 95% CI = 3.3%-84%) and PTE-related mortality (OR = 9.4, 95% CI = 4.1%-21.5%). The mortalities of PTE patients with normal and abnormal troponin levels were 3.7% and 19.7% [27]. The Meta-analysis of three PE patients with stable hemodynamics showed that the short-term mortality was significantly associated with the troponin (RR = 8.3%, 95 CI = 3.6%-19.3%), the sensitivity of mortality prediction was 81%, the negative predictive value was 73%, and the positive predictive value was 75% [20]. The long-term follow-up of this study found that the plasma troponin levels might reflect the long-term prognosis. Moreover, Stein et al. [28] and Thielmann et al [29] also found that the combination of cTnI positive and right ventricular dilation had a higher value towards the PTE prognosis. The troponin was the sensitive and specific indicator that could evaluate the ischemic myocardial injury, when this value increased, the mortality also significantly increased.

In addition, age, basic diseases (cancer, heart failure, hyperlipidemia, chronic lung disease, etc.), poor control and DVT could all affect the

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long-term prognosis of PTE patients [16, 20]. Certain prospective study had already demonstrated that the simultaneous existence of ultrasound diagnosed deep venous thrombosis was an independent predictor of poor prognosis towards the PE patients, and compared with the patients without deep vein thrombosis, the short-term overall mortality and PE-related mortality of former PE patients were increased by 2 to 4 times [30]. The univariate analysis of this study found that the above factors could affect the occurrence of re-embolism, death and CTEPH, but the multivariate analysis revealed no statistical significance among these factors, which needed the larger clinical studies in future to further confirm its role in the PTE prognosis.

In summary, this study and a number of domestic and foreign studies all considered that the idiopathic PTe, RVD, D-dimer positive, anticoagulation treatment < 3 months, cTnI positive and post-treatment PASP > 40 mmHg were the important factors that would affect the long-term prognosis towards the PTE patients. Besides the effective anticoagulant therapy, the patients with the above factors should be performed the essential appropriate precautions and active education.

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Disclosure of conflict of interest

None.

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