International Journal of Cardiology 202 (2016) 275–281

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Pulmonary embolism risk stratification by European Society of Cardiology is associated with recurrent venous thromboembolism: Findings from a long-term follow-up study

Shuai Zhang [a,b,1], Zhenguo Zhai [a,b,1], Yuanhua Yang [a,b,1], Jianguo Zhu [c], Tuguang Kuang [a,b], Wanmu Xie [a,b], Suqiao Yang [a,b], Fangfang Liu [a,b], Juanni Gong [a,b], Ying H. Shen [d], Chen Wang [c,e,f,*]

[a] Beijing Institute of Respiratory Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, PR China
[b] Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing, PR China
[c] National Clinical Research Center of Respiratory Medicine, Beijing, PR China
[d] Department of Cardiothoracic Surgery, Baylor College of Medicine, Houston, USA
[e] China-Japan Friendship Hospital, Beijing, PR China
[f] Department of Respiratory Medicine, Capital Medical University, Beijing, PR China

ARTICLE INFO

Article history:
Received 25 March 2014
Received in revised form 29 August 2014
Accepted 27 September 2014
Available online 5 October 2014

Keywords:
Pulmonary embolism
Venous thromboembolism
Recurrence
Risk stratification
Prognosis
European Society of Cardiology

ABSTRACT

Venous thromboembolism (VTE) recurrence carries significant mortality and morbidity. Accurate risk assessment and effective treatment for patients with acute pulmonary embolism (PE) is important for VTE recurrence prevention. We examined the association of VTE recurrence with risk stratification and PE treatment. We enrolled 627 patients with a first episode of confirmed PE. Baseline clinical information was collected. PE severity was assessed by the European Society of Cardiology's (ESC) risk stratification, the simplified PE Severity Index (sPESI) and the Qanadli score of clot burden. Patients were followed for 1–5 years. The cumulative recurrent VTE and all-cause death were documented. The association between recurrent VTE and risk factors was analyzed. The cumulative incidences of recurrent VTE were 4.5%, 7.3%, and 13.9% at 1, 2, and 5 years of follow-up, respectively. The VTE recurrence was associated with higher (high- and intermediate-) risk stratification predicted by ESC model (HR 1.838, 95% CI 1.318–2.571, P < 0.001), as well as with unprovoked PE (HR 2.809, 95% CI 1.650–4.781, P b 0.001) and varicose veins (HR 4.747, 95% CI 2.634–8.557, P < 0.001). The recurrence was negatively associated with longer (≥6 months) anticoagulation (HR 0.473, 95% CI 0.285–0.787, P = 0.004), especially in patients with higher risk (HR 0.394, 95% CI 0.211–0.736, P = 0.003) and unprovoked PE (HR 0.248, 95% CI 0.122–0.504, P < 0.001). ESC high-risk and intermediate-risk PE, unprovoked PE and varicose veins increase recurrence risk. Longer anticoagulation treatment reduces recurrence, especially in higher risk and unprovoked PE patients.

1. Introduction

Recurrent venous thromboembolism (VTE) occurs in 20%–30% of the patients with acute pulmonary embolism (PE) or deep venous thrombosis (DVT) within 5 years of the first thrombotic event [1]. Recurrent VTE is fatal in 4%–11.5% of patients [2,3]. Patients with recurrent VTE need prolonged or even lifelong anticoagulation therapy [4,5] which increases the patients' financial burden, inconvenience and risk of bleeding. The incidence of diagnosed PE has increased recently in China [6]. However, the VTE recurrence in China, or even in Asia, has not been clearly evaluated and reported.

High morbidity and poor clinical outcomes associated with VTE recurrence require accurate and rapid risk assessment for acute PE patients. Several risk factors for VTE recurrence have been identified, including advanced age [3], male gender [7,8], unprovoked VTE [3,9,10], thrombophilia [3], obesity [11], and persistent elevation of D-dimer 1 month after discontinuation of anticoagulation [12,13] and residual thrombosis [14]. In contrast, prolonged oral anticoagulation therapy reduces VTE recurrence [15]. The severity of the initial VTE is associated with early mortality [5] and combined adverse outcome [16]. However, its effect on VTE recurrence is less clear.

Risk stratification has been recommended in clinical guidelines to predict the early prognosis of acute PE. Several models including the European Society of Cardiology (ESC) risk stratification [5], Pulmonary Embolism Severity Index (PESI) [17], simplified PESI (sPESI) [18], Pulmonary Arterial Obstruction Index (PAOI) [19], Qanadli score of clot burden [20], and Vienna Prediction Model [21] have been

* Corresponding author at: China-Japan Friendship Hospital, 2 Yinghua East Street, Beijing 100029, PR China.
E-mail address: cyh-birm@263.net (C. Wang).
[1] These authors contributed equally to this article.

http://dx.doi.org/10.1016/j.ijcard.2014.09.142
0167-5273/

developed. ESC risk stratification has been used to show that in the first month, high- and intermediate-risk PE patients have higher mortality than low-risk patients [5]. The ESC model showed better accuracy than PESI in identifying high-risk and low-risk patients [22] by predicting all-cause and PE-related in-hospital mortality. However, whether these models can be used to predict the late recurrence remains to be determined.

In the present prospective study, we followed 627 patients with a first episode of acute PE for 1–5 years. The incidence of recurrent VTE was documented and its association with risk factors was analyzed. The association between the long-term VTE recurrence and disease severity (assessed by ESC risk stratification, sPESI and Qanadli score) was also evaluated.

2. Methods

2.1. Study population

We enrolled consecutive patients with acute PE in Beijing Chao-Yang Hospital, a national reference hospital, from January 2006 to March 2011. This study was approved by the Institutional Review Board of Beijing Chao-Yang Hospital.

The inclusion criteria were acute symptomatic PE with or without DVT, confirmed by at least one of the following examinations: computed tomography pulmonary angiography (CTPA), ventilation/perfusion lung scan (V/Q scan), pulmonary arteriography (PA) and magnetic resonance pulmonary angiography (MRPA). Patients with previous history of symptomatic PE or a life expectancy of less than 3 months were excluded. Clinical information was recorded in a standardized case report form based on the original medical records.

PE without the following risk factors are classified as unprovoked PE [5]: recent surgery, trauma, immobilization for more than three days, recent long immobility, deep venous catheterization, pregnancy or peripartum period, oral contraceptives administration or female hormone replacement therapy, active malignancy, chronic heart or respiratory failure, cerebrovascular disease, nephrotic syndrome, obesity and varicose veins.

2.2. Risk stratification

2.2.1. ESC risk stratification

The study population was categorized into three groups according to the ESC risk stratification model [5]: high-risk patients with signs of shock or hypotension, intermediate-risk patients who were normotensive with right ventricular dysfunction (RVD) and/or myocardial injury, and low-risk patients who were normotensive without RVD or myocardial injury. Indications of RVD included RV dilatation (basal diameter > 42 mm), hypokinesis, or pressure overload on echocardiography (the presence of ≥1 of four signs: (i) right-sided cardiac thrombus; (ii) RV diastolic dimension (parasternal view) ≥30 mm or a RV/LV ratio > 1; (iii) systolic flattening of the interventricular septum; and (iv) acceleration time <90 ms or tricuspid insufficiency pressure gradient > 30 mm Hg without RV hypertrophy) [5], RV dilatation (RV/LV ≥ 1) on CTPA, elevated right heart pressure at right heart catheterization, and elevated plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) greater than 84 pg/ml. Markers of myocardial injury included plasma cardiac troponin I greater than 0.09 ng/ml.

2.2.2. sPESI

The sPESI score [18] was calculated for all the patients. One point was assigned for each of these variables: age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate >110 beats/min, systemic systolic blood pressure <100 mm Hg, and arterial oxyhemoglobin saturation <90%. Patients with none of these variables (0 point) were categorized as low-risk, and those with a score of ≥1 were high-risk.

2.2.3. Clot burden assessment

We used the Qanadli score [20] in CTPA to assess the clot burden. The arterial tree of each lung was divided into 10 segments. The presence of embolus in a segmental artery was scored 1 point, and embolus in the most proximal arterial level was scored a value equal to the number of segmental arteries arising distally. The Qanadli score was expressed as: $\Sigma\,(n \cdot d) / 40 \times 100\%$, where n was the value of the proximal thrombus equal to the number of segmental branches arising distally (minimum, 1; maximum, 20), and d was the degree of obstruction (0 with no thrombus; 1 with partial occlusion; or 2, with total occlusion).

2.3. Treatment

All the patients were hospitalized for the initial treatment. ESC high-risk and selected intermediate-risk PE patients without any absolute contraindications received thrombolytic therapy, while low-risk patients received anticoagulation therapy only. All treatment decisions were determined according to the ESC guidelines [5]. Patients received either intravenous unfractionated heparin sodium with dose adjustments to achieve activated partial thromboplastin time (APTT) of 1.5 to 2.5 times the control value; or twice-daily body weight-adjusted doses of subcutaneous low-molecular-weight heparin (LMWH). Vitamin K antagonist (warfarin) was initiated on the first day of treatment with heparin, with a target international normalized ratio (INR) of 2.0 to 3.0.

Patients with PE secondary to a transient risk factor received warfarin treatment for at least 3 months. Patients with PE secondary to a permanent risk factor or with unprovoked PE received anticoagulation for at least 6 months. Indefinite treatment was recommended for most patients with a recurrent unprovoked DVT or PE.

2.4. Follow-up and clinical endpoints

The patients were followed at 3, 6, 12, 24, 36, and 60 months after the initial PE event in the outpatient department. When patients could not return to hospital for follow-up, they were interviewed by telephone. Patients with suspected recurrence were asked to return to hospital and received comprehensive assessment. These patients underwent a V/Q lung scan or CTPA, followed by PA when necessary [23]. Recurrent PE was distinguished from chronic thromboembolic pulmonary hypertension (CTEPH) by the acute onset, the presence of fresh thrombus in imaging examinations, and the absence of right ventricular hypertrophy in echocardiogram. Recurrent DVT was confirmed by computed tomography venography (CTV) with a new intraluminal filling defect in two different projections. Compression venous ultrasonography criteria for recurrent DVT were incompressibility of a proximal vein segment previously free of thrombi, or an increase of the vein diameter by more than 4 mm compared with the last available measurement [24]. In the case of a high clinical probability but negative ultrasound findings, CTV was performed to rule out isolated iliac or calf vein thrombosis. All the recurrent events and all-cause deaths were documented, and were adjudicated by an independent adjudication committee composed of physicians and radiologists.

Clinically relevant bleeding was defined as clinically overt bleeding episodes such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, hemoptysis, hematuria, epistaxis or gingival bleeding.

2.5. Statistical analysis

All the analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD), median and quartile, or frequency, depending on the variable. Independent *T*-test and one-way ANOVA were used to compare mean of normally distributed data, while nonparametric tests were used to compare abnormally distributed or discrete data. χ^2 test was used to compare categorical data. A Kaplan–Meier life-table method was used to calculate the cumulative incidence of recurrent VTE and death. Cox proportional hazards regression model was used to identify the risk factors for VTE recurrence and death. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were reported.

3. Results

3.1. Patient characteristics

In 681 consecutive patients diagnosed with acute PE, six patients had a history of previous symptomatic PE, three patients had a life-expectancy of less than 3 months, and 45 patients dropped out of the follow-up, mainly due to the loss of contact or unwillingness to follow

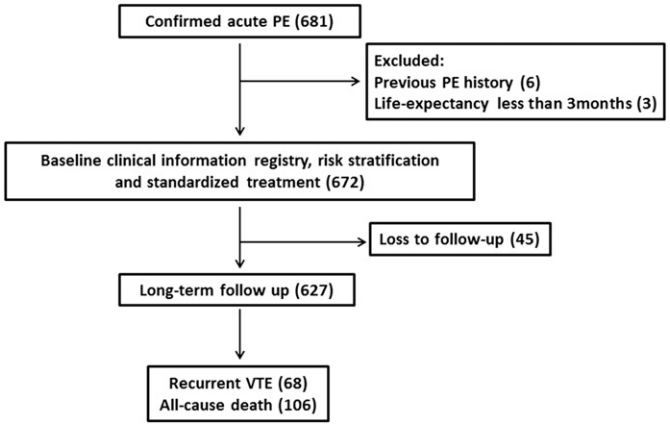

Fig. 1. In 681 consecutive patients diagnosed as acute PE, 6 patients had a history of previous symptomatic PE, 3 patients had a life-expectancy of less than 3 months, and 45 patients dropped out of the follow-up. 627 consecutive patients were enrolled and followed up after discharged from hospital. During the follow-up period, 68 patients had symptomatic VTE recurrence. 106 patients died.