

Clinical feature analysis of fatal pulmonary thromboembolism: experiences from 41 autopsy-confirmed cases

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Abstract. – **AIM:** Due to non-specific symptoms and imaging features, a timely and accurate diagnosis of pulmonary thromboembolism (PTE) is often difficult. This study aims to evaluate the frequency of, and risk factors for, autopsy-confirmed cases with fatal pulmonary thromboembolism (FPE) that were missed or misdiagnosed before death.

MATERIAL AND METHODS: Forensic autopsies that were performed at the Center of Forensic Medicine in West China were retrospectively reviewed, and demographic and clinical data of autopsy-confirmed cases with FPE were collected.

RESULTS: There were 41 cases with pathologically confirmed FPE, which represents 7.3% (41/558) of autopsy cases that documented sudden death in hospital. Of those 41 cases, only 14.6% (6/41) were correctly diagnosed before death, and 85.4% (35/41) were missed or misdiagnosed. According to medical records, bowel movements and out-of-bed activity were the major triggers of FPE death, and 90% of cases had at least two of the known risk factors for PTE. Increasing age, orthopedic surgery, and multiple traumas were the most common risk factors. Additionally, of the 41 cases with FPE, 51.2% (21/41) died in the Orthopedic Department.

CONCLUSIONS: FPE was common in older patients who had a recent history of surgery and multiple traumas. Increasing the early diagnosis of PTE in high-risk patients may be useful for reducing the incidence of FPE.

Key Words:

Pulmonary embolism, Thrombosis, Sudden death, Orthopedic surgery, Multiple traumas.

suffer an acute PE event, and 10% of them die PE¹⁻³. As the most common type of PE, pulmonary thromboembolism (PTE) has become the third most common life-threatening disease, second only to malignant tumors and myocardial infarctions⁴. Recent data have shown that the overall fatality rate of PTE is 20-30% for patients without therapeutic interventions, but only 2-8% for patients who received prompt effective treatment⁵⁻⁷.

In recent years, significant advancements have been made in the management of PTE. However, due to the non-specific symptoms and imaging features, a timely and accurate diagnosis of PTE is still challenging, and the majority of cases are either missed or misdiagnosed⁸⁻¹², while only approximately 10-30% of cases could have been diagnosed before death¹³. It is estimated that about half of the sudden, unexpected deaths of fatal pulmonary thromboembolism (FPE) occur within one hour of the onset of symptoms, and the diagnosis of FPE was always made after autopsy⁹⁻¹¹.

Although some prospective studies have provided insights into the risks of PTE, there remains a paucity of data in the literature describing the prevalence or clinical characteristics of hospitalized patients suffering fatal VTE events. In this study, we evaluate the frequency and risk factors for autopsy-confirmed cases of FPE that were missed or misdiagnosed before death, in the hope of providing a reference for reducing the incidence of FPE in future clinical practice.

Patients and Methods

Patients and Study Design

Forensic autopsy files stored in the Center of Forensic Medicine in West China from January 2001 and December 2010 were screened, and on-

Introduction

Data indicate that pulmonary embolism (PE) is a common disorder. Each year in the United States (US), approximately 600,000 individuals

ly hospital deaths with autopsy-confirmed FPE were reviewed comprehensively. The following data were collected according to our pre-designed survey form: demographic information, medical history before death (including major illnesses, any recent surgery or trauma, and any ongoing illness), clinical diagnosis, and patients' activities, signs or symptoms before death.

The survey forms were completed by both forensic pathologists and physicians, who were rigorously trained for the research approach, investigational content, quality control, and filling out the survey form. The investigation record for each case was checked by a physician before statistical analysis was undertaken.

Definition of FPE

The frequency of FPE was estimated from extrapolated data obtained during autopsy. Hospital deaths that fulfilled the following criteria were considered for FPE:

1. Death was associated with acute cardiopulmonary arrest or rapidly progressing respiratory failure, and PE was found in the proximal pulmonary arteries at autopsy.
2. The clinical and pathological data indicated that the patient would not have died of his or her underlying disease at that time if PE had not occurred.

Sections of all organs of hospital deaths were stained with haematoxylin, eosin, and Masson's trichrome, and a forensic pathological diagnosis of PE was made by three pathologists after discussion.

Data Analysis

All data were managed and analyzed using the Statistical Package for the Social Sciences version 13.0 software (SPSS Inc., Chicago, IL, USA). Quantitative data were presented as the mean \pm standard deviation (SD), and categorical data were presented as counts and percentages.

Results

Prevalence of FBT

As shown in Figure 1, 2,081 forensic autopsies were performed, with 73.2% (1,523/2,081) of deaths occurring outside hospital and 26.8% (558/2,081) of deaths occurring in hospital. Of the 70 sudden deaths caused by PE among the

558 hospital deaths, there were 41 cases with FPE, which represented 7.3% (41/558) of autopsy cases in the hospital. Of those cases with FPE, only 14.6% of cases (6/41) were diagnosed with PE before death, of which four cases had preventability anticoagulation drugs for thrombosis, while 30 cases were misdiagnosed (including 15 cases as coronary heart disease, nine cases as pulmonary infection, and six cases as heart failure) and five cases involved amissed diagnosis.

Among the 41 autopsy-confirmed cases with FPE, 34 cases (82.9%) were massive PE, two cases (4.9%) had thrombi occluding the proximal right pulmonary artery, two cases (4.9%) had thrombi occluding the proximal left pulmonary artery, and the cases (7.3%) were observed in the presence of thrombotic material occluding segmentary branches in both lungs. In 25 cases (61.0%), the thrombus originated in the deep venous system of lower limbs, including 15 in the right calf, eight in the left calf, and two in the right thigh. In 16 cases (39.0%), the origin of the thrombus was not identified.

Clinical Features Prior to Death

Of the 41 autopsy-confirmed cases with FPE, there were 35 cases (85.4%) with shortness of breath, 24 cases (58.5%) with shock, 23 cases (56.1%) with cyanosis, 20 cases (48.8%) with chest pain, four cases (9.7%) with fever, and four cases (9.7%) with hemoptysis. Additionally, 12 cases (29.3%) complained of pain in the lower limbs on the day prior to death.

The above symptoms and signs appeared suddenly, and the disease progressed rapidly. The time of onset to death ranged from 15 minutes to 23 hours. In relation to inducements of FPE, 90.2% (37/41) of those cases prior to death had defecation, turning over, and out-of-bed movement.

Potential Risk Factors

Potential risk factors are shown in Table I. All patients had risk factors: 95.1% of cases had two or more risk factors and 70.7% of cases had three or more risk factors.

Of the 41 cases with FPE, 26 cases (63.4%) were men and 15 cases (36.6%) were women, which represented a male-female ratio of 1.7:1. The mean age was 58.9 ± 18.4 years, ranging from 22 to 74 years for men and 6 to 79 years for women. There were 27 cases (65.8%) over the age of 40, which indicated that increasing age might be a potential risk factor.

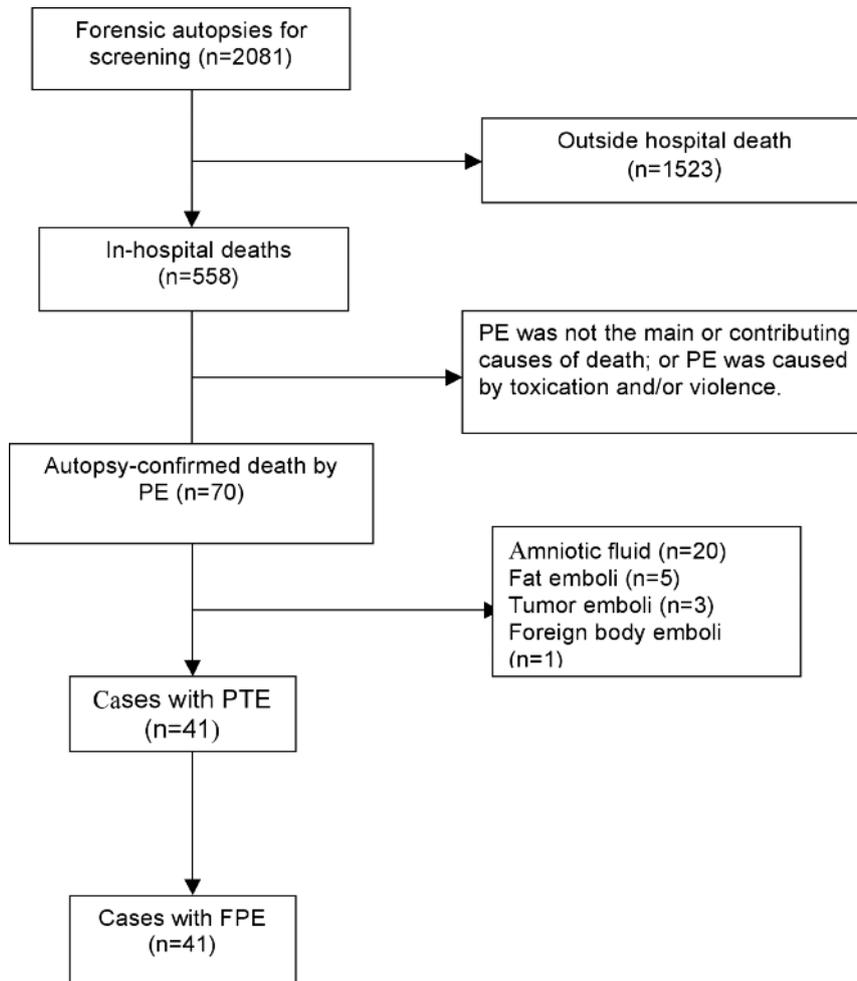


Figure 1. Flow chart for the screening of forensic autopsies.

Prior to death, the majority of the cases were admitted to Surgical Departments, particularly the Orthopedic Department. Of the 41 cases, 30 (73.2%) suffered multiple traumas and 34 (82.9%) underwent surgeries. Of the 34 cases who underwent surgeries, 21 cases comprised fractures with internal fixation or joint replacement, which accounted for 51.2% (21/41) of the cases. Autopsy results showed that FPE was observed in 76.5% (26/34) and 56.7% (17/30) of cases within the first seven days (cases ranged from three to 24 days) after surgeries and multiple traumas, respectively, and four cases were of sudden death during surgery. Thus, it was necessary to take certain measures to prevent the occurrence of PE for patients who underwent surgeries or suffered multiple traumas.

In relation to illnesses before death, autopsy results suggested that 73.2% of cases had dis-

eases, which included 24.4% (10/41) with diabetes mellitus, 17.1% (7/41) with hypertension, 19.5% (8/41) with coronary heart disease, 9.8% (4/41) with pulmonary infection, and 2.4% (1/41) with kidney disease. The data indicated that patients with concomitant diabetes mellitus and/or hypertension might have an increased risk of PE.

Obesity or high body mass index (BMI) was not common in the present study. Of the 41 cases with FPE, 22 cases had accurate information regarding BMI, and only two cases had a BMI greater than 25 kg/m², but without obesity.

Discussion

Many risk factors related to PE have been discovered that could cause vascular endothelial damage, stasis of blood flow, and hypercoagula-

Table I. Risk factors observed in 41 cases of fatal PTE.

Risk factor	Observations	Number of cases (%)
Overweight and obesity	Overweight (2), obesity (0)	2/22 [#] (9.1)
Surgery		
Major surgery	Orthopedic (21), abdomen (5) Obstetrical (5), chest (1)	32/41 (78.0)
Minor surgery		2/41 (4.9)
Multiple trauma		30/41 (73.2)
Age ≥ 40 years		27/41 (65.85)
Hypertension		7/41 (17.1)
Coronary heart disease		8/41 (19.5)
Type 2 diabetes mellitus		4/41 (9.6)
Pregnancy and postpartum		6/41 (14.6)
History of venous thromboembolism		1/41 (2.4)
Immobilization		24/41 (58.5)
Pulmonary infection		4/41 (9.6)
Varicose veins		2/41 (4.9)
Kidney disease		1/41 (2.4)
One or more risks		100
Two or more risks		95.1
Three or more risks		70.7

Note: [#]Indicates that the data for 19 cases were inefficient (six cases were pregnant women and 13 cases were without adequate measurements).

bility of blood. Currently, trauma has been regarded as one high-risk factor of PE due to direct vascular injuries, blood clotting caused by post-traumatic stress, and the subsequent application of tourniquets and fixed measures¹⁴⁻¹⁶. As reported, the prevalence rate of PTE in patients after trauma ranged from 0.4% to 18%, with an estimated fatality rate of 17% to 26%¹⁷⁻²⁰. However, there is a scarce amount of data regarding multiple traumas in FPE. In the present study, we found that multiple traumas occurred in 73.2% of cases that died in FPE.

It is usually considered that pulmonary emboli occurred most commonly between five to seven days after injury²¹, while one recent report showed that 37% of PE cases could occur in the first four days after trauma¹⁹. Unfortunately, the period of death caused by PE after trauma was rarely described. In this study, we first reported that the death by PE occurred between three to 24 days after injury, and 56.7% of cases occurred in the first week after trauma. Therefore, it is reasonable to infer that non-fatal PTE may have already formed in the early stages after trauma has occurred. Physicians should increase the awareness of the early diagnosis of PE and pay more attention to the thrombosis.

Studies from both autopsies and clinical cohort studies showed that surgery increased the risk of PTE, and the risk was closely related to the type

and duration of surgeries^{22,23}. Previous works have reported that orthopedic and major abdominal surgeries had a higher risk of PTE than other types of surgeries^{24,25}. Compared to approximately 0.3-1.6% of PE in the general surgical population, the prevalence of PE after a hip fracture repair was 4.3-24%, and the prevalence of FPE was 3.6-12.9%^{15,25-27}. In addition, the type and duration of anesthesia during surgery were also considered risk factors for the occurrence of PE^{28,29}. In our study, 82.9% (34/41) of cases had a history of recent surgery, and the majority of those cases were orthopedic surgery patients, where 76.5% of deaths occurred in the first seven days after surgery. Similarly, Wroblewski et al's investigation showed that 91% of fatal pulmonary emboli formed within 28 days of total hip arthroplasties, with 71% occurring in the second post-operative week^{23,30}. Thus, it is easy to see that surgical departments (particularly major surgery) should pay close attention pre-operatively, and establish earlier preventions for those who have accumulative risk factors.

Numerous studies have reported that the incidence of PTE is associated with increasing age. Patients over 40 years of age had a higher incidence of PTE than did younger patients and, for each 10-year increase in age, the incidence of PTE doubled³¹⁻³³. In the present research, there were 27 cases over 40 years of age, which represented 65.9% of the total number of cases, and suggests

that FPE occurs mainly in elderly patients. In Europe and the US, obesity has been regarded as a risk factor for PTE³¹⁻³⁴. However, obesity cases did not exist in our study, and this finding would be associated with the race of patients. Thus, obesity or a high BMI index might not be considered an important factor of PTE for Asian patients.

Previous data have reported that symptoms or signs of PE before death were often deficient or non-specific. Due to similar clinical manifestations, it was difficult to distinguish PE from coronary heart disease, myocardial infarction, pneumonia, pulmonary emphysema, and congestive heart failure. Thus, missed diagnosis and misdiagnosis of PE is common in clinical practice^{8,35-37}. In the present study, 85.4% (35/40) of cases with PE could not be timely and accurately diagnosed, resulting in sudden and unexpected death caused by PTE. It has been reported that the misdiagnosis rate of PE was 67-73% in the US and around 80% in China, and few patients received timely treatment³⁷⁻³⁹. While the diagnosis and management of PE has developed in recent years, an accurate and timely diagnosis is still challenging for clinicians. At present, the causes of misdiagnosis are mainly related to the following factors:

- A lack of awareness and vigilance for PE
- A lack of adequate knowledge of underlying diseases and incentives related to PE
- Non-specific clinical manifestations of PTE
- Relying on auxiliary examination excessively, lacking of full analysis.

Conclusions

Surgical departments have a relatively high incidence of FPE, particularly for older patients with multiple traumas and surgeries, and the occurrence rate of FPE is high in the early stages after surgery and/or multiple traumas.

Doctors are encouraged to learn about the formation of emboli in older patients with multiple traumas and surgeries, and to give proper and effective prevention and treatment as early as possible.

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