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Brief communication (Original)

Etiologies and treatment of acute pulmonary embolism at Srinagarind Hospital

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Background: The incidence of acute pulmonary embolism has been increasing over the past few years. Prevention, early detection and appropriate treatment will decrease morbidity and mortality.
***Objective*:** We identified the etiologies and treatment outcomes of acute pulmonary embolism.
Methods: We enrolled hospitalized patients diagnosed with acute pulmonary embolism at Srinagarind Hospital between January 1, 2002 and October 31, 2009.
Results: Over the eight-year period, 169 patients were diagnosed with acute pulmonary embolism; 95 (56.2%) females and 74 (43.8%) males. The mean age was 54.1 years (range, 18-85). 13% presented with massive pulmonary embolism. The most common presentation was dyspnea (65.1%). Arterial hypoxemia (88.8%) and sinus tachycardia (58.3%) were the common initial clinical findings. Twenty percent of chest radiograph were unremarkable. The most common etiology was cancer (62.1%), mostly solid malignancies (98/105) e.g., cholangiocarcinoma, gynecologic malignancy, and lung cancer. The second and the third common etiologies were immobilization/stasis (8.3%) and connective tissue disease (7.1%). After treatment, 58.6% of the patients improved while 21.3% died in hospital. The main therapeutic modality was anticoagulation. The treated group had better outcomes than those receiving only supportive care. Only one patient underwent thromboembolectomy but died. The complications during treatment were acute respiratory failure (34.9%), shock (18.3%), and bleeding (6.5%).
Conclusions: The most common etiology of acute pulmonary embolism was cancer, especially solid malignancies. Immobilization and connective tissue disease were the other common etiologies. The treatment group had a better prognosis than those with supportive care only

Keywords: Acute pulmonary embolism, etiology, outcome

The incidence of acute pulmonary embolism in Thailand was thought to be low in past decades. However, diagnosis of acute pulmonary embolism has been increasing and clinician's awareness of this disease is improving [1]. Massive pulmonary embolism may lead to sudden death. The known risk factors for acute pulmonary embolism can be divided into hereditary and acquired factors. The most common hereditary factor is factor V Leiden, which causes activated protein C resistance. The other causes are deficiencies in protein C, protein S, and antithrombin III. These usually occur in young patients with an unusual location of deep vein thrombosis (DVT). The most commonly acquired factor is reduced mobility and cancer. Other causes are oral contraceptives, trauma, obesity, central venous catheterization, and antiphospholipid syndromes.

A report from Japanese medical patients indicated that 62% (83/133) of acute pulmonary embolism had prolonged immobilization [2]. Stroke (28%), cancer (24%), indwelling central venous catheter (20%), and obesity (17%) were common risk factors. Previous data from Thailand indicated that 42.2% (30/71) of acute pulmonary embolism patients had no identified risk factors [3]. Among the known risk factors, malignancy, especially adenocarcinoma were the most common (21%), followed by DVT (18.3%) and immobilization (15.5%). Many risk factors can be prevented and the outcome improved with early diagnosis and management. The objective of this study was to identify the common etiologies and clinical

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outcomes of acute pulmonary embolism at Srinagarind Hospital, a tertiary care hospital in the Northeast of Thailand.

Materials and methods

This was a cross-sectional study. We enrolled hospitalized patients diagnosed with acute pulmonary embolism at Srinagarind Hospital between 1 January 2002 and 31 October 2009. The diagnostic criteria were; 1) sudden dyspnea with arterial hypoxemia; 2) high probability by V/Q scan and/or pulmonary embolism identified by CT angiogram. We excluded children age <15 years of age and patients with acute arterial hypoxemia due to other conditions (e.g., congestive heart failure, pneumonia, and acute alveolar hemorrhage). Cases with arterial hypoxemia and hypotension (blood pressure <90/60 mmHg) were diagnosed as having massive pulmonary embolism.

The data record form included; age, sex, occupation, initial symptoms and signs, underlying diseases, and laboratory finding. Final investigations to ascertain the etiologies of acute pulmonary embolism were collected. Patients received treatment such as thrombolytic therapy, heparin, oral anticoagulant and thromboembolectomy. The outcomes of treatment, length of hospitalization and complications were also recorded.

The study protocols were approved by the Ethics Committee of the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. Descriptive statistics were used to describe the data. Means and SD were calculated for the continuous data, number and percentage for the categorical data.

Results

Over the eight-year period, 169 patients were hospitalized at Srinagarind Hospital with a diagnosis of pulmonary embolism. Of these, 22 patients (13%) presented with massive pulmonary embolism. The demographic data were shown in **Table 1**. The mean age was 54.1 (SD 15.6) years, and the male to female ratio was 1:1.3. One-third of the patients' occupation was farmer and twenty-three percent were retired. The major underlying diseases were cancer (59.8%) and DVT (55.6%). Only one patient had underlying thalassemia, which is interesting since it is a common genetic condition in Northeast of Thailand.

The average duration of symptoms was 2.8 (SD 2.4) days (**Table 1**). The prominent symptom was acute dyspnea found in 65.1% of the patients. Pleuritic chest pain was present in 14.8%, hemoptysis in 5.9% and leg swelling in 39.1%

Table 1. Patients' characteristics and clinical manifestations

Characteristic and clinical manifestation	N=169
Age (mean, SD) (days)	54.1 (15.6)
Sex (male:female)	1:1.3
Occupation (N, %)	
- Farmer	50 (29.6%)
- Retire	39 (23.1%)
- Civil service	27 (16.0%)
- Private business	13 (7.7%)
- Other	40 (23.7%)
Underlying disease (N, %)	160 (94.7%)
- Cancer	101 (59.8%)
- Deep vein thrombosis	94 (55.6%)
- Immobilization	38 (22.5%)
- Connective tissue disease	12 (7.1%)
- Non-tuberculous mycobacteria/ TB/ HIV	5 (3.0%)
- Nephrotic syndrome	3 (1.8%)
- Thalassemia	1 (0.6%)
Duration (mean, SD) (days)	2.8 (2.4)
Symptoms and signs (N, %)	
- Dyspnea	110 (65.1%)
- Pleuritic chest pain	25 (14.8%)
- Hypotension	22 (13%)
- Hemoptysis	10 (5.9%)
- Leg swelling	66 (39.1%)

The most common initial laboratory finding was arterial hypoxemia (**Table 2**). Arterial blood gas was determined in 152 patients and 88.8% had arterial hypoxemia. Sinus tachycardia (58.3%) and $S_1Q_3T_3$ (32.6%) were the most frequent ECG findings. Most chest X-rays were unremarkable (20.1%), followed by unilateral pleural effusion (18.9%), localized infiltration (13.8%), prominent pulmonary trunk (13.2%), atelectasis (6.3%), localized oligemia (5.0%) and wedge shape infiltration (1.9%). D-dimer levels were positive in 97 of 104 patients (93.3%). Ventilation/perfusion lung scintigraphy was performed on 140 patients and 120 patients (86.0%) had a high probability result. Acute pulmonary embolism was confirmed by CT angiogram in only 53 patients and 49 patients (92.4%) had a positive result.

The final etiologies were identified in 145 patients (85.8%) as shown in **Table 3**. The most common etiology of acute pulmonary embolism was cancer, 105 patients (62.1%). Of these, 98 patients had solid malignancies and seven patients had hematologic malignancies. Cholangiocarcinomas (33), gynecologic malignancy (20) and lung cancer (10) were common causes of solid malignancies. On the other hand, lymphoma (6), and multiple myeloma (1) were the common causes of hematologic malignancies.

Table 2. Initial laboratory findings

Laboratory finding	Percentage
Arterial blood gas	
- Arterial hypoxemia	88.8% (135/152)
Electro-cardio gram	
- Sinus tachycardia	58.3% (84/144)
- $S_1Q_3T_3$	32.6% (47/144)
Chest X-ray	
- Normal	20.1% (32/159)
- Unilateral pleural effusion	18.9% (30/159)
- Localized infiltration	13.8% (22/159)
- Prominent pulmonary trunk	13.2% (21/159)
- Atelectasis	6.3% (10/159)
- Localized oligemia	5.0% (8/159)
- Wedge shape infiltration	1.9% (3/159)
Positive D-dimer	93.3% (97/104)
V/Q scan	
- High probability	86.0% (120/140)
CT angiogram	
- Positive result	92.4% (49/53)

Table 3. Etiologies of acute pulmonary embolism

Etiology of acute pulmonary embolism	N=169
Cancer	105 (62.1%)
Immobilization/Stasis	14 (8.3%)
Connective tissue disease	12 (7.1%)
Protein C/ Protein S deficiency	4 (2.4%)
Obesity	3 (1.8%)
Nephrotic syndrome	2 (1.2%)
Septic embolism	1 (0.6%)
Fat embolism	1 (0.6%)
Tetralogy of Fallot status post Blalock Taussig shunt embolism	1 (0.6%)
Non-tuberculous mycobacteria	1 (0.6%)
HIV	1 (0.6%)
Unknown	24 (14.2%)

The second most common etiology was immobilization (8.3%) due to cerebrovascular accident (6), bed ridden (3), fracture femur/knee (3), and post operative surgery (2). The third most common etiologies were connective tissue diseases (7.1%) including antiphospholipid syndrome, systemic lupus erythrematosus (SLE), polymyositis and diffuse systemic sclerosis. The fourth common etiology was protein C and/or protein S deficiency (2.4%). Obesity and nephrotic syndrome were found in 1.8% and 1.2% of the patients, respectively.

Other uncommon causes were one each of septic embolism, fat embolism, Tetralogy of Fallot post Blalock Taussig shunt embolism, non-tuberculous mycobacteria (NTM) and HIV infection.

Management of the patients was divided into five groups according to severity and underlying diseases (**Table 4**). In cases of massive pulmonary embolism and no contraindication to thrombolytic therapy, the patients received thrombolytic therapy followed by unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Only three of these six patients (50%) recovered.

The main treatment of our patients was heparin (UFH/LMWH) and 138 patients (81.7%) initially received this treatment. Sixty-five percent showed clinical improvement, while 16.7% did not improve and 18.1% died. Oral anticoagulant was administered to five patients and 80% showed clinical improvement. Only one patient underwent thromboembolectomy and died. Nineteen patients had supportive care only, most of them clinical worst and died.

Overall hospitalization averaged 18.7 days. Complications during treatment were respiratory failure needing mechanical ventilation (34.9%), shock (18.3%), and bleeding (6.5%).

Discussion

Our results showed that acute pulmonary embolism is not uncommon in Thailand as previously believed. It was slightly more common in middle age females, similar to a report from Korea, where acute pulmonary embolism was more frequent among women than men and in patients over 50 years of age [4]. Most of the patients had at least one identified underlying disease and in more than half it was cancer. This finding indicated that malignancy predisposed patients to acute pulmonary embolism which has an increasing rate in Thailand. Previous reports indicated that it ranged between 10% and 21% [3, 5]. Patients with cancer have an increased risk of venous thromboembolism compared with patients without cancer [6].

In a Chinese study, more than one-third (37.5%) of 120 patients with solid malignancy were non-small cell lung cancer, presumably due to the high rate of smokers [6]. By comparison, 105 of our patients had cancer and in 31.4% it was cholangiocarcinoma; a common malignancy in Northeast of Thailand due to the consumption of raw fish infested with liver flukes.

The second most common cause of solid malignancy in our study was gynecologic cancer, mostly of cervix, ovary and endometrium. Lung cancer, which was a common finding in china, ranked third in our study. Hematologic malignancy (e.g., lymphoma and multiple myeloma) occurred in only seven cases.

Patients with medical comorbidities, especially cerebrovascular accidents, and being bed ridden had a high prevalence of DVT. Consequently, the American College of Chest Physicians (ACCP) recommends primary prophylaxis of venous thromboembolism for this medically compromised population [7]. However, according to the DVT

Table 4. Results of treatment

Treatment	Total	Outcome (%)			Hospitalization
		Improve	Not improve	Death	Mean (SD) day
Combination thrombolytic and UFH/LMWH	6	3 (50%)	3 (50%)	0 (0%)	43 (53.8)
UFH/LMWH	138	90 (65.2%)	23 (16.7%)	25 (18.1%)	17.9 (16.6)
Oral anticoagulant	5	4 (80%)	1 (20%)	0 (0%)	26.8 (35.0)
Thromboembolectomy	1	0 (0%)	0 (0%)	1 (100%)	54
Supportive care	19	2 (10.5%)	7 (36.8%)	10 (52.6%)	12.4 (19)
Total	169	99 (58.6%)	34 (20.1%)	36 (21.3%)	18.7 (19.7)

UFH=unfractionated heparin, LMWH=low molecular weight heparin

Registry, only 42% of such inpatients in America received appropriate prophylaxis [8], indicating an underutilization problem. In Thailand, primary prophylaxis of venous thromboembolism in medically compromised patients is not widely used because it is thought that the prevalence of acute pulmonary embolism is very low which we have shown is not true. Prolonged bed rest or immobilization usually occurs in fractures of lower extremities and post operative surgery, particular after abdominal operation and trauma. This was the most common cause of acute pulmonary embolism [9]. Early ambulation and mobilization should be encouraged for this group of patients.

Antiphospholipid syndrome and SLE with heavy proteinuria are common causes of acute pulmonary embolism in connective tissue disease. However, acute pulmonary embolism from connective tissue disease is not a common finding. It occurred in less than ten percent of our study. The antiphospholipid syndrome, leading to massive pulmonary embolism and sudden death is very rare [10].

The clinical presentation of sudden dyspnea, pleuritic chest pain and leg swelling among our patients did not differ from other studies [5, 9]. Among patients with such warning signs chest x-ray, ECG, arterial blood gases and D-dimer testing should be promptly carried out. A definite diagnosis of acute pulmonary embolism can then be derived by ventilation-perfusion scan (V/Q) and/or detection of thrombus in pulmonary trunk on a CT angiogram [11]. In critically-ill patients, especially those on mechanical ventilator, an acute pulmonary embolism may be difficult to diagnose [12]. This diagnosis should be considered if such a patient develops sudden episodes of hypotension, tachycardia, or unexplained hypoxemia. If pulmonary embolism remains unsuspected in such a patient the condition will progress to a fatal outcome.

Since the most common etiology for acute pulmonary embolism in our study was a solid malignancy, treatment modalities were limited by known adverse events from thrombolytic and/or anticoagulation therapy in this group of subjects. Twenty-two patients presented with massive pulmonary embolism, but only six received thrombolytic therapy followed by UFH/LMWH. One-half survived the acute episode. Emergency echocardiography and/or a CT angiogram followed by immediate thrombolysis should be the treatment of massive pulmonary embolism [13]. If a patients had a contraindication for thrombolysis, the alternative treatments includes catheter directed lysis and/or pulmonary embolectomy [14, 15]. The mortality rate for massive pulmonary embolism with hemodynamic compromise is high, rising up to 70% within the first hour of presentation [15]. In our study only one patient underwent emergency thromboembolectomy but died.

Patients with cancer receiving anticoagulant are more likely to develop recurrent venous thromboembolism. A meta-analysis showed statistically significant mortality reduction in patients treated with LMWH compared with those treated with UFH (RR=0.71, 95% CI 0.52 to 0.96) [16]. Continued low molecular weight heparin for six months is more effective than warfarin in the secondary prevention of venous thromboembolism in cancer patients and this without increasing the risk of bleeding. It is the preferred treatment option [17].

Management of venous thromboembolism in patients with cancer changed over the past decade, leading to improved outcome and quality of life. Unfractionated heparin (UFH) and oral vitamin K antagonists (warfarin) were the mainstay of management of venous thromboembolism in the mid-twentieth century, followed by the widespread replacement of UFH by low molecular weight heparin (LMWH) in the 1990s. In the near future, the new classes of oral anticoagulants that directly inhibit specific clotting factor targets (e.g., thrombin and factor Xa) may be the preferred management of venous thromboembolism in patients with cancer. In our study, the treatment group, which received thrombolytic therapy or UFH/LMWH or oral anticoagulants, had a better prognosis than those receiving only supportive care. The risk of bleeding was present in only 6.5% of patients.

Conclusion

Acute pulmonary embolism is a major cause of death in patients with known risk factors or underlying diseases. It is now diagnosed more frequently in Thailand where the incidence is not significantly different from Western countries. The most common underlying risk factor in our hospital was malignancy; particularly solid cancers such as cholangiocarcinoma, gynecologic malignancy and lung cancer. Patients with immobilization due to cerebrovascular accidents and being bed ridden and those with fractures of the lower extremities were also common. Connective tissue diseases should also be considered, especially the

antiphospholipid syndrome and systemic lupus erythrematosus, the latter being quite common in Thailand. Treatment of acute pulmonary embolism has improved dramatically and patients who received timely treatment have a better prognosis than those who received no specific treatment or suffer significant delay in diagnosis and management.

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