Original Article

Pulmonary Embolism: Treatment Outcomes and Prognostic Factors of Mortality in University Hospital

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Objective: To determine the treatment outcomes, and to identify the prognostic factors of hospital mortality of pulmonary embolism (PE) patients.

Materials and Methods: A retrospective cohort study was conducted in a 1,400-bed university hospital. Demographic, Medical history, clinical data and treatment outcomes were collected. Logistic regression was performed to identify prognostic factors for all-cause of hospital mortality.

Results: One hundred fifty-eight patients with PE were included, 47.5% were male and the mean age was 59.2±14.7 years. The most common of clinical presentation are dyspnea 125 (79.1%), tachycardia 72 (45.6%), and hypotension 39 (24.7%). Forty patients (25.3%) had acute massive PE. The overall mortality rate (MR) was 19.6% and intensive care unit (ICU) MR was found in 34.5%. The prognostic factors of mortality were massive PE (adjusted odds ratio [AOR] 5.44, 95% confidence interval [CI] 1.10 to 27.06, p=0.039), cancer (AOR 4.45, 95% CI 1.52 to 12.98, p=0.006), respiratory failure (AOR 3.63, 95% CI 1.10 to 12.10, p=0.019), and SOFA score of 5 or greater (AOR 3.46, 95% CI 1.11 to 10.80, p=0.032).

Conclusion: PE is associated with high mortality in hospital, especially in ICU. The prognostic factors for hospital mortality were massive PE, respiratory failure, cancer comorbidity and SOFA score of 5 or greater.

Keywords: Pulmonary embolism, Prognostic factor, Mortality, Treatment outcomes

Received 17 June 2020 | Revised 14 October 2020 | Accepted 15 October 2020

J Med Assoc Thai 2021;104(2):225-32

Website: http://www.jmatonline.com

Acute pulmonary embolism (PE) is one of the leading causes of sudden cardiac arrest. The high morbidity and mortality are responsive to hemodynamic instability and respiratory failure[1,2]. The incidence of venous thrombosis and PE reported from Europe in 2008 was approximately 50 to 100 per 100,000 population[3], Australia was 30 per 100,000 population, and in Korea was 229 per 100,000 population[4]. The incidence of suspected PE was higher in critically ill patients approximately 0.4% to 2.3%[5]. The mortality rate (MR) of PE patients who developed shock ranges from 16% to 30%, and patients with cardiac arrest ranges from 52% to 77%[6-8]. Most deaths in patients presenting with shock occurred within the first hour of presentation and caused from delayed diagnosis and treatment[8,9]. However, the mortality can be reduced to 8% in cases of early appropriated diagnoses and treatment[10]. A previous study reported the clinical predictors for fatal PE were massive PE, immobilization for neurological disease, cancer, and age older than 75 years[11]. Even though the MR of PE in Thailand had been reported in 2002 at 20.1%[12], the data regarding prognostic factors of mortality among PE in Thailand are limited. Therefore, the objectives of the present study were to determine the clinical presentation, treatment outcomes of intensive care unit (ICU) and hospitalized patients with PE, and to identify the prognostic factors of all-cause mortality in patients with PE.

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How to cite this article:

Inchai J, Pothirat C, Liwsrisakun C, Euathrongchit J, Tajareunmuang P, Rerkasem K. Pulmonary Embolism: Treatment Outcomes and Prognostic Factors of Mortality in University Hospital. J Med Assoc Thai 2021;104:225-32.

doi.org/10.35755/jmedassocthai.2021.02.11545

Materials and Methods

Study design, setting

A retrospective cohort study of admitted PE patients was conducted in the tertiary care, 1,400-bed Chiang Mai University Hospital, Chiang Mai, Thailand between 2014 and 2016. The study was

approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (certificate of approval No. 469/2016).

Participants

All admitted PE that registered in the hospital database between 2014 and 2016 were retrospectively reviewed. Inclusion criteria were 18 years or older and PE. PE was diagnosed by clinical suspicious PE, including dyspnea or hypoxemia unexplained by lung parenchyma, airway disease, or heart failure. Imaging including abnormalities of echocardiography compatible with acute PE and confirmed diagnosis by computed tomography pulmonary angiography (CTPA). The authors excluded chronic thromboembolic pulmonary hypertension (CTEPH), chronic PE. All CTPA were performed with 64 slices dual source multidetector CT scans [Somatom Definition (Siemens, Forchheim, Germany)] while using low or iso-osmolar nonionic contrast material injected though basilic vein at rate of 4 mL/second. The delay time between injection and scanning was done by using bolus tracking. Scanning was performed from the diaphragm to lung apex, detector collimation was 0.6 mm, slice thickness was 0.75 mm, pitch was 0.8 mm, voltage was 120 kVp, effective mAs was 200 mA, rotation time was 0.33 second, and using Kernel B20f and PE window.

Data collection

Source document obtained from Medical record and Electronic medical record in Suandok Medical Information System (SMI). Demographic data included gender, age, and comorbidity. Acute PE has classified to massive PE and submassive PE. Massive PE is defined as PE with hemodynamic unstable with a systolic blood pressure [SBP] of less than 90 mmHg, shock, or cardiac arrest, and submassive PE is defined when there is an evidence of right ventricular (RV) dysfunction but hemodynamic stable with a SBP of 90 mmHg or higher[2,3]. Medical history, clinical signs and symptoms, risk of PE, evidence of shock, echocardiographic that indicating RV dysfunction, CTPA confirmed of acute PE, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, ICU admitted, mechanical ventilator (MV) required and duration, hospital length of stay, PE management (including medical, surgical or others), treatment outcomes, and adverse outcome of occurrence of bleeding were also recorded. The authors also categorized organ failure that required ICU admission included respiratory failure as acute respiratory failure that needed for ventilator support, either invasive or non-invasive. Hemodynamic unstable was defined as hypotension requiring fluid resuscitation or vasopressors to maintain mean arterial pressure (MAP) of 65 mmHg or higher.

Outcomes measure

The outcome was all course of hospital mortality. The patient status at ICU and hospital discharge were also evaluated. All PE patients were followed up for survival status until hospital discharge.

Statistical analysis

Data were compared between the survival and non-survival group. Categorical variables were expressed as number and percentage, and were analyzed using the chi-square or Fisher's exact test. Continuous variables were expressed as mean and standard deviation or median and interquartile range (IQR), and were compared using Student t-test or Wilcoxon rank sum test as appropriate of data distribution verified by Kolmogorov-Smirnov test. Univariable and Multivariable logistic regression were performed to identify the prognostic factors of hospital mortality. The odds ratio (OR) and its 95% confidence intervals (CI) were estimated. Variables with a p-value of less than 0.10 in univariable analysis and those considered clinically relevant were included in multivariable analysis using enter selection. All p-values were two-tailed, and a p-value of less than 0.05 was considered to be statistically significant. All statistical analysis was performed using Stata, version 14.0 (StataCorp LP, College Station, TX, USA).

Results

Between 2014 and 2016, 215 patients were reported as PE in the hospital database with ICD-10 I26, of whom 158 were confirmed with PE that met the inclusion criteria of the present study. Fifty-seven patients (26.5%) were excluded due to the exclusion criteria. At hospital discharge, there were 127 survivors and 31 non-survivors. The MR was 19.6%.

Characteristics and treatment outcomes of PE

One hundred fifty-eight PE patients were included in this study. The gender was 47.5% male, and the mean age was 59.2±14.7 years. PE was diagnosed by clinical and confirmed by CTPA in all patients, however, echocardiogram was performed in 80 (50.6%) patients. Seventy-four (48.8%) patients

Table 1. Patient characteristics of PE

Variables	All case (n=158); n (%)	Survivor (n=127); n (%)	Non-survivor (n=31); n (%)	p-value
Sex: male	75 (47.5)	60 (47.2)	15 (48.4)	0.909
Age (years); mean±SD	59.2±14.7	59.5±14.7	58.2±14.6	0.659
Co-morbidity				
Cancer	79 (50.0)	58 (45.7)	21(67.7)	0.028
Diabetes mellitus	22 (13.9)	17 (13.4)	5 (16.1)	0.692
Cardiovascular disease	20 (12.6)	17 (14.3)	3 (9.7)	0.542
Chronic kidney disease	11 (7.0)	8 (6.3)	3 (9.7)	0.507
Cirrhosis	9 (5.7)	5 (3.9)	4 (12.9)	0.053
COPD	8 (5.9)	7 (5.5)	1 (3.2)	0.603
Current smoker	19 (14.1)	13 (10.2)	6 (19.3)	0.125
Site of care before admission				
Emergency room	74 (48.8)	58 (45.7)	16 (64.5)	0.818
Outpatient department	47 (29.7)	39 (30.7)	8 (25.8)	
Refer case	37 (23.4)	30 (23.6)	7 (22.6)	
Ward of admission				
Medical	122 (77.2)	99 (78.0)	13 (41.9)	0.762
Surgical	19 (12.0)	16 (12.6)	3 (9.7)	
Orthopedics	6 (3.8)	4 (3.2)	2 (6.5)	
Gynecology	5 (3.2)	4 (3.2)	1 (3.2)	
Admission in ICU	58 (36.7)	38 (29.9)	20 (64.5)	<0.001
APACHE II score; mean±SD	13.0±6.3	11.8±5.6	18.3±6.8	<0.001
SOFA score; median (IQR)	2 (2, 5)	2 (2, 4)	6 (4, 9)	<0.001

COPD=chronic obstructive pulmonary disease; ICU=intensive care unit; APACHE II=acute physiology and chronic health evaluation II; SOFA=sequential organ failure assessment; SD=standard deviation; IQR=interquartile range

were admitted from emergency department. Forty patients (25.3%) were compatible with acute massive PE and 119 (75.3%) patients were submissive PE. Eighty-five percent of the patients had co-morbidities including 79 patients (50.0%) with malignancy and 22 (13.9%) with diabetes mellitus. The most common clinical presentation was dyspnea in 125 (79.1%), followed by tachycardia 72 (45.6%), and altered consciousness 31 (19.6%). The risk factors for acute PE included malignancy 79 (50.0%), recent surgery 34 (21.5%), and history of DVT 27 (17.1%). D-dimer was collected in 70 patients with median of 5,816 ng/mL (2,235 to 13,123 ng/mL). APACHE II score at the day of onset was 12.8±6.2 and SOFA score 2 (IQR 2, 5). Fifty-eight patients (36.7%) were admitted in ICU due to respiratory failure in 47 (81.0%) and hemodynamic unstable in 34 (58.6%) (Table 1, 2).

Treatment outcomes

In the present study, eight cases (5.0%) received only supportive treatments due to cardiac arrest and sudden death at emergency department in three cases and bleeding contraindication for anticoagulant in five cases. Most of all, 143 (90.5%) received medical treatment including anticoagulant with unfractionated heparin (UFH) intravenous administration or low molecular weight heparin (LMWH) 135 (94.4%) and eight patients (5.6%) in 39 acute massive PE received thrombolysis drug with alteplase (rt-PA) in four cases and streptokinase in four cases. Seven patients (5.1%) underwent pulmonary embolectomy or endarterectomy. Treatment outcomes, classified by treatment group, revealed highest MR in supportive treatment (87.5%), follow by medical and surgical group (16.8% and 0%, respectively), as shown in Table 3. Sixty-eight patients (30.4%) required MV support for a median duration of 4 (1 to 11) days. The length of ICU and hospital stay were 5.0 (2 to 11) days and 11 (5 to 23) days, respectively. Bleeding complication after treatment was found in 27 patients (17.1%). There were four patients with massive PE that developed fatal gastrointestinal bleeding including one case post thrombolysis medication, and three cases post anticoagulant drug.

Table 2. Risk factors and clinical presentation of PE

	All case (n=158); n (%)	Survivor (n=127); n (%)	Non-survivor (n=31); n (%)	p-value
Risk of PE				
Heart failure or MI	10 (6.3)	8 (6.3)	2 (6.5)	0.975
Recent surgery	34 (21.5)	28 (22.0)	6 (19.4)	0.744
History of VTE	27 (17.1)	22 (17.3)	5 (16.1)	0.874
Cancer risk	79 (50.0)	58 (45.7)	21(67.7)	0.028
Stroke weakness or bed ridden	20 (12.7)	16 (12.6)	4 (12.9)	0.964
Obesity	3 (1.9)	3 (2.4)	0 (0.0)	0.388
Clinical presentation				
Dyspnea	125 (79.1)	97 (76.4)	28 (90.3)	0.087
Respiratory failure required MV support	48 (30.4)	27 (21.3)	21 (67.7)	<0.001
Hypotension	39 (24.7)	21 (16.5)	18 (58.1)	<0.001
Tachycardia	72 (45.6)	52 (40.9)	21 (67.7)	0.047
Alternative of conscious	31 (19.6)	19 (15.0)	12 (38.7)	0.003
Chest pain	13 (8.2)	12 (9.4)	1 (3.2)	0.075
Hemoptysis	6 (3.8)	3 (2.4)	3 (9.7)	0.056
Lower extremity swelling	41 (25.9)	33 (26.0)	8 (25.8)	0.984
D-dimer level (ng/mL), median (IQR)	5,816 (2,235, 13,123)	5,173 (2,158, 25,701)	7,662 (4,725, 15,657)	0.493
PE classification*				<0.001
Submassive PE	118 (74.7)	105 (82.7)	13 (41.9)	
Massive PE	40 (25.3)	22 (17.3)	18 (58.1)	
Bleeding complication	27 (17.1)	18 (14.2)	9 (29.0)	0.049

PE=pulmonary embolism; MI=myocardial infarction; VTE=venous thromboembolism; MV=mechanical ventilator; IQR=interquartile range

* Massive PE: acute PE with shock or cardiac arrest, Submassive PE: acute PE with hemodynamic stable

Table 3. Treatment outcomes and MR of PE patients (total n=158)

Treatments	All	MR; n (%)
Medication	143	24 (16.8)
Anticoagulant (UFH/LMWH)	135	22 (16.3)
Thrombolytic + anticoagulant	8	2 (25.0)
Surgery: embolectomy/endarterectomy	7	0 (0.0)
Supportive care	8	7 (87.5)
Overall hospital MR	158	31 (19.6)
ICU MR	58	20 (34.5)
Hospital LOS (day); median (IQR)	11 (5, 23)	
ICU LOS (day); median (IQR)	5 (2, 11)	
MV (day); median (IQR)	4 (1, 11)	

MR=mortality rate; UFH=unfractionate heparin; LMWH=low molecular weight heparin; MV=mechanical ventilator; LOS=length of stay; ICU=intensive care unit; IQR=interquartile range

Prognostic factors of mortality

The overall hospital MR was 19.6% (31/158), including five that died within 24 hours after admission. Regarding 58 cases admitted in ICU, the ICU MR was 34.5% (20/58). The univariable analysis demonstrated that cancer, cirrhosis, respiratory failure, massive PE, APACHE II, SOFA score of 5 or more, and bleeding complication as well as being older than 75 years were considered as potential predictors of hospital mortality. The independent prognostic factors of hospital mortality identified by multivariable analysis were massive PE (adjusted odds ratio [AOR] 5.44, 95% CI 1.10 to 27.06, p=0.039), cancer comorbidity (AOR 4.45, 95% CI 1.52 to 12.98, p=0.006), respiratory failure (AOR 3.63, 95% CI 1.10 to 12.10, p=0.019), and SOFA score of 5 or more (AOR 3.46, 95% CI 1.11 to 10.80, p=0.032), as shown in Table 4.

Discussion

Clinical presentation

Acute PE is an emergency medical condition. The common symptoms of the present study patients included dyspnea, tachycardia, lower extremity swelling, and alternative consciousness, which are similar to the reports from the previous studies[13-17]. One fourth (25.3%) of the patients were initially diagnosed massive PE, which alternative of

Table 4. Prognostic factors of hospital mortality of PE patients by using univariable and multivariable logistic regression (total n=158)

Predictors	Univariable		Multivariable	
	OR (95% CI)	p-value	AOR (95% CI)	p-value
Sex: male	0.95 (0.43 to 2.09)	0.909		
Age >75 years	1.10 (0.34 to 3.60)	0.867	1.51 (0.31 to 7.40)	0.612
Comorbidities				
Cancer	2.49 (1.09 to 5.73)	0.031	4.45 (1.52 to 12.98)	0.006
Diabetes mellitus	1.24 (0.42 to 3.68)	0.693		
Cardiovascular disease	0.32 (0.04 to 2.55)	0.282		
Chronic kidney disease	1.59 (0.40 to 6.39)	0.511		
Cirrhosis	3.61 (0.91 to 14.36)	0.068	2.10 (0.35 to 12.54)	0.416
COPD	0.57 (0.07 to 4.82)	0.607		
Current smoker	4.93 (0.64 to 37.82)	0.125		
Respiratory failure	7.78 (3.27 to 18.46)	<0.001	3.36 (1.10 to 12.10)	0.036
Massive PE	6.98 (2.97 to 16.40)	<0.001	5.44 (1.10 to 27.06)	0.039
APACHE II	1.14 (1.07 to 1.21)	<0.001	1.05 (0.96 to 1.14)	0.308
SOFA score ≥5	6.73 (2.88 to 15.35)	<0.001	3.47 (1.11 to 10.81)	0.032
Bleeding complication	3.19 (1.35 to 7.54)	0.008	1.25 (0.42 to 3.77)	0.686

COPD=chronic obstructive pulmonary disease; APACHE II=acute physiology and chronic health evaluation II; SOFA=sequential organ failure assessment; OR=odds ratio; AOR=adjusted odds ratio; CI=confidence interval

consciousness from hypoperfusion are predominant presentations. Chest pain, which is usually pleurisy in nature, is a result of distal emboli occlusion leading to pulmonary infarction and pleural irritation[18]. Blood clots (thrombi) generally originate form one of the deep veins of the legs, thighs, and pelvic cavity. This condition is known as venous thromboembolism (VTE)[2]. The authors also found that the risk factors of acute PE were consistent with previous reports, cancer is the highest risk factor, followed by recent surgery, and history of VTE[13]. In the present study, D-dimer was high but tested in only one-fourth (25.3%). In general practice in the authors' hospital, D-dimer was tested in case of clinical low suspected of PE, while most patients in the present study were highly suspected of acute PE leading to investigation by using imaging as guideline. However, the previous reported, D-dimer testing is not useful for diagnosis of acute PE in high-risk patient with high clinical suspicion because of its low specificity[18,19].

Treatment

In the present study, most of the patients received anticoagulant including unfractionate heparin (UFH) intravenous administration or LMWH. MR in anticoagulant group was found in 16.8%. The guidelines of European Society of Cardiology (ESC) and American College of Chest Physicians (ACCP) suggests that thrombolysis with alteplase (rt-PA), streptokinase, or urokinase is the recommended treatment of massive-high risk PE. In non-massive intermediate risk PE, thrombolysis has been proposed in selected patients at high risk for adverse outcomes[18,20,21]. The authors found only eight patients (20.5%) in massive PE that received thrombolysis with four cases alteplase (rt-PA), and four cases of streptokinase, because most patients were with shock and persistent arterial hypotension. The MR in the present group was found in 25% (2/8), higher than the report of Meneveau et al, which found MR in patients who received thrombolytic treatment at only 8.8%[22]. Meta-analysis demonstrated that thrombolysis therapy can decrease mortality and recurrence of PE when compared with heparin in patient with acute PE. However intracranial hemorrhage was reported 3% to 4%[23,24]. The present study found seven patients (5.1%) that had surgery for embolectomy or endarterectomy because the medication with either anticoagulant or thrombolytic therapy was contraindicated. All of them were survived. Embolectomy is indicated an alternative therapy for PE patients with shock in the acute setting when thrombolysis is contraindicated[9,25,26].

However, the authors found eight patients that received only supportive treatment such as blood

transfusion, hemodynamic, and respiratory support. Seven patients died (MR of 87.5%) due to three patients had sudden cardiac arrest at emergency department and four patients had bleeding contraindication for anticoagulant or thrombolytic therapy.

Mortality

The overall hospital MR of PE patients in the present study was quite high at 19.6%, especially in patients admitted in ICU, with an MR of 34.5% (20/58). These are higher than the previous study in Europe and North America that found all-cause MR between 9% to 17%[11,27] and report of Park et al from Korea was 7.8%[4]. The high MR found in the present study can be explained by the high risk of death in patients presented with massive PE with shock, severity of the patients by high APACHE II score, and most have one or more organ failure on date of PE onset. It also probably related to the underlying disease such as malignancy. Moreover, 64.5% of death cases were severe and admitted to ICU due to respiratory failure, and hemodynamic instability, as shown in Table 1.

Prognostic factors

The prognostic factors of hospital mortality in the present study included massive PE, malignancy comorbidity, respiratory failure, and SOFA score of 5 or more. These were comparable to the previous studies that reported malignancy comorbidity, altered of conscious, shock, and cancer comorbidity were associated with mortality[6,27-29]. According to classification of PE, variables of altered of conscious and hypotension or shock were observed as massive PE, so the authors excluded those variables from multivariable logistic regression analysis to prevent multicollinerity in the final model.

The clinical data such as older age, underlying diseases, including malignancy, chronic kidney disease, chronic obstructive pulmonary disease (COPD), immunocompromised status, and hepatic disease, have also been reported as prognostic indicators of hospital mortality[5,11,14,16,18,27-29]. These factors were evaluated by univariable analysis in the present study; however, malignancy was the only independent predictor of mortality identified following multivariate analysis. The present study data corroborate to the previous studies, a multivariate analysis of 570 patients with PE, comorbidity with cancer was increased risk of mortality, progression to shock, or recurrence of PE[13]. Similar to the study of Gussoni et al (RIETE registry), the three-month mortality of PE patients with and without cancer were 26.4% and 4.1%. Among over 35,000 VTE patients, cancer was the strongest independent factor for both of PE-related and all-cause mortality[30]. In-hospital mortality was related to the severity of PE as defined by massive PE, in particular organ dysfunction such as hemodynamic instability, and respiratory failure. The previous study demonstrated illness severity (high APACHE II and SOFA score) shock, mechanical ventilation, and the presence of multi-organ failure as independent risk factors for mortality[3,5,6,28]. Olivier Sanchez et al reported the prognostic factor of mortality were shock on admission (OR 2.8, 95% CI 1.1 to 7.5) and cancer (OR 2.9, 95% CI 1.2 to 6.9)[13]. Klok et al also reported cancer as an independent factor of mortality (HR 4.4, 95% CI 2.0 to 10)[6].

The present study had some limitations. Firstly, the study was conducted at a single university hospital, therefore, the results may not be in-keeping with national epidemiologic data. Secondly, the study did not report attributable PE mortality, only all-cause mortality. Thirdly, the present study was a retrospective study, had incomplete data for some factors potentially related to mortality including time to start medication, and compliance to PE guidelines were not monitored. Further prospective studies are required to fully evaluate prognostic factors of mortality among PE patients.

Conclusion

PE is associated with high mortality in hospital, especially in ICU. The independent prognostic factors for hospital mortality were massive PE, respiratory failure, cancer comorbidity, and SOFA score of 5 or more.

What is already known on this topic?

PE is a cause of sudden cardiac arrest that associated with increased morbidity and mortality. Although, there have been reports of incidence and outcomes of PE from the previous studies, there are limited data of predictors on hospital mortality of PE patients in Thailand.

What this study adds?

The prognostic factors of hospital mortality of PE in this study included massive PE, malignancy comorbidity, respiratory failure, and SOFA score of 5 or more. The findings are useful to establish the further clinical practice guidelines for management for PE's patients with those predictors.

Acknowledgement

This study was supported by NCD center, Research Institute of Health Science, Chiang Mai University.

Conflicts of interest

The authors declare no conflict of interest.

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