

Cancer Associated Acute Pulmonary Embolism: A Six-years' Experience from a Single Center of Thailand

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Background: Cancer is the most prevalent triggering condition for acute pulmonary embolism (PE). Characteristics and treatment outcomes could be varied among practices.

Objective: To study the characteristics, treatments, and outcomes of patients with cancer-associated acute PE.

Materials and Methods: All patients admitted with acute PE from January 2011 to December 2016 were retrospectively recruited into Khon Kaen University Pulmonary Embolism (KKU PE) registry, and patients with cancer-associated acute PE were subsequently enrolled in the present analysis. Clinical characteristics, biomarkers, imaging, treatments, and in-hospital courses were reviewed. Survival was followed until December 31st, 2018.

Results: 188 out of 347 patients (54.2%) enrolled in KKU PE registry were classified as cancer associated acute PE. Among those patients, median age (interquartile range) was 61 (18 to 87) years, and 105 patients (55.9%) were female. PE was classified as low risk, sub-massive, and massive in 49 (26.1%), 125 (66.5%), and 14 (7.4%) patients, respectively. Cholangiocarcinoma (CCA), gynecologic malignancies, and lung cancer were most of the associated cancers (49 (26.1%), 35 (18.4%), and 26 (13.8%) patients, respectively). Acute PE was diagnosed in 75 patients during their hospital admission. Systemic thrombolysis was given in 3 patients (21.4%) with massive PE and in 6 patients (3.4%) with non-massive PE, ($p=0.001$). Initial parenteral anticoagulants were given in 162 patients (86.2%), and long-term oral anticoagulants were given in 67 patients (35.6%). Five patients (2.7%) underwent transcatheter treatment and no patient underwent surgical thromboembolectomy. Major bleeding and intracranial bleeding occurred in 12 patients (6.5%) and 1 patient (0.5%), respectively. The mean survival (95% confidence interval) of overall patients was 11.8 (8.3 to 15.3) months.

Conclusion: Cancer is the most common risk factor for acute PE and CCA is the most prevalent associated cancer. Treatment, either medication or intervention, seemed to be underutilized, and prognosis of cancer associated acute PE was grave.

Keywords: Pulmonary embolism; Venous thromboembolism; Cancer; Malignancy

Received 17 February 2025 | Revised 14 May 2025 | Accepted 14 May 2025

J Med Assoc Thai 2025; 108(Suppl.2):S130-136

Website: <http://www.jmatonline.com>

Acute pulmonary embolism (PE) remains one of the leading causes of death due to acute cardiovascular disease worldwide⁽¹⁾. It is one part of the spectrum of venous thromboembolism (VTE), which deep venous thrombosis (DVT) is composed in another part^(2,3). A combination of endogenous and exogenous provoking factors plays an important role in the formation of clots inside the deep

venous system, which eventually traverses through the right heart to occlude the pulmonary artery and results in acute right ventricular failure^(4,5).

Association between cancer and VTE had been revealed for a long time⁽⁶⁾, and its role as a trigger for acute PE is seemingly more prominent in the recent era^(7,8). Active cancer accounts for about 20% of incident VTE patients^(9,10). Studies in Thai patients who were admitted due to medical conditions found that cancer was a significant risk factor for VTE, in which over 50% of patients developed VTE in hospital, had concomitant active cancer^(11,12). Interestingly, about 10% of patients with newly diagnosed acute PE had previously unknown cancer or had a new cancer diagnosis short time later⁽¹⁰⁾. Treatment concept for acute PE in patients with active cancer is mostly similar to patients with no active cancer⁽³⁾. However, a recent COPE study had found the significantly increased risks of death and major bleeding at 30 days in patients with PE who had active cancer compared with those who had previous cancer or

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How to cite this article:

Intarasattakul P, Dangploy T, Leeprakobboon W, Aueyingsak S, Pussadhamma B. Cancer Associated Acute Pulmonary Embolism: A Six-years' Experience from a Single Center of Thailand. *J Med Assoc Thai* 2025; 108(Suppl.2):S130-136.

DOI: 10.35755/jmedassocthai.2025.S02.S130-S136

who had no cancer⁽¹³⁾.

The characteristics of the patients, treatments, and outcomes of treatments of cancer-associated acute PE may be varied according to the types of cancer and the availability and expertise of treatments of acute PE in each circumstance of patients and practices. In the present study, the authors aimed to study the characteristics of the patients, treatments, and outcomes of patients with cancer-associated acute PE during a recent practice at our center.

Materials and Methods

Previously, the authors conducted the Khon Kaen University Pulmonary Embolism (KKU PE) registry, in which all consecutive adult patients admitted with the diagnosis of acute PE at Srinagarind Hospital and Queen Sirikit Heart Center of the Northeast from January 1st, 2011 to December 31st, 2016, were retrospectively enrolled. In the present study, all patients from the KKU PE registry, in whom the diagnosis of cancer-associated acute PE was made, were included for the analysis. The inclusion criteria were: 1) aged above 18 years old, 2) being diagnosed with active cancer of any type, and 3) being diagnosed with acute PE, confirmed by computed tomography pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) scan. Baseline patients' information, clinical characteristics, biomarkers, imaging studies, and acute PE-related treatments were reviewed from the medical records and electronic medical database. Massive PE was defined as PE that resulted in hemodynamic instability, specifically shock or hypotension, sub-massive PE was defined as PE with evidence of right ventricular dysfunction in the absence of hemodynamic compromise, and low-risk PE was defined as PE with hemodynamically stable and without evidence of right ventricular dysfunction⁽¹³⁾. The primary outcome was in-hospital major bleeding which was defined as a composite of fatal bleeding, internal organ bleeding, or bleeding with required blood component transfusion. The secondary outcome was survival of patients which was followed until December 31st, 2018. The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research (HE591150).

Statistical analysis

The continuous variables were presented as median and interquartile range (IQR). The categorical variables were presented as numbers and percentages. Student's t-test was used to compare continuous variables between subgroup massive PE and non-massive PE when appropriated, and the Chi-square test was used to compare the categorical variables. Survival analysis was conducted using the Kaplan-Meier survival curve. Survival time from date of PE diagnosis to death or until December 31st, 2018 (date

of censoring) in each group was compared using Log Rank (Mantel-Cox) test. All statistical analyses were performed using SPSS version 19.0. The p-value of less than 0.05 indicated a statistically significant difference.

Results

Of the 347 patients enrolled in KKU PE registry, 188 patients (54.2%) were classified as cancer-associated acute PE. Among patients with cancer-associated acute PE, the median age (interquartile range, IQR) was 61 (18 to 87) years, and 105 patients (55.9%) were female. Patients were covered by the universal coverage (UC) scheme in 95 patients (51.9%). Recent immobilization was the most common predisposing factor for acute PE (50 patients, 27.0%), whereas previous VTE was found in 15 patients (8.0%). The duration of symptoms was markedly varied, with the median (IQR) of 72 (0.5 to 2,160) hours. Dyspnea was the most common presenting symptom (96 patients, 55.8%). DVT was found in over 47 patients (27.3%). Sub-massive or intermediate risk PE was the most prevalent PE classification in 125 patients (66.5%), while massive or high-risk PE was in 14 patients (7.4%). According to the types of cancer, cholangiocarcinoma (CCA) was the most prevalent cancer found to be related with acute PE (49 patients, 26.1%), followed by gynecologic cancer and lung cancer in 35 patients (18.6%), and 26 patients (13.8%), respectively. Almost 40% of patients developed acute PE while being admitted for the initial reason other than acute PE (in-hospital PE). The characteristics of the patients were described in Table 1.

Systemic thrombolysis was given in 9 patients, 8 of whom received alteplase. The systemic thrombolysis was more often used in massive PE than non-massive PE, 3 out of 14 (21.4%) and 6 out of 174 (3.4%), ($p=0.001$), respectively. The parenteral anticoagulants were used dominantly in patients with non-massive PE ($n=56.4\%$), with Enoxaparin being the most prevalent used ($n=60.3\%$), but the unfractionated heparin (UFH) was more often used in patients with massive PE ($n=71.4\%$) ($p<0.001$). Fondaparinux was not used in any patients. Oral anticoagulants were used in 67 patients (35.6%), 65 of whom (97.0%) received warfarin. Regarding the intervention therapy, 5 patients (2.7%) underwent transcatheter therapy. None of the patients received treatment with surgical thromboembolism. Major bleeding occurred in 12 patients (6.5%), and fatal bleeding occurred in 1 patient (0.5%). There was no significant difference in bleeding between subgroup massive PE and non-massive PE ($p>0.999$). Treatments and bleeding outcomes were shown in Table 2.

Details of patients' characteristics, treatments, and bleeding outcomes for each type of cancer were in Table 3.

Table 1. The characteristics of the patients with cancer-associated acute pulmonary embolism

Characteristics	
Age (years)	61 (18 to 87)
Female, n (%)	105 (55.9)
BMI (kg/m ²)	22.63 (12.8 to 37.2)
Health care coverage, n (%)	
UC	95 (51.9)
SSS	11 (6.0)
CSMBS	73 (39.9)
Other	4 (2.2)
Underlying diseases/risk factors, n (%)	
Diabetes mellitus	25 (13.3)
Hypertension	49 (26.1)
Previous VTE	15 (8.0)
Use of HRT	0
Recent fracture	9 (4.8)
Recent surgery	22 (11.8)
Recent critical care admission	21 (11.3)
Recent immobilization	50 (27.0)
Indwelling venous catheter	6 (3.2)
Duration of symptom (hours)	72 (0.5 to 2,160)
Clinical presentation – n (%)	
Dyspnea	96 (55.8)
Chest pain	12 (7.7)
Syncope	2 (1.3)
Shock/hypotension	10 (6.2)
Cardiac arrest	11 (6.7)
Sign of DVT	47 (27.3)
D-dimer (mcg/L)	6,363 (285 to 40,441)
Classification of acute PE – n (%)	
Low risk	49 (26.1)
Sub-massive	125 (66.5)
Massive	14 (7.4)
In-hospital PE – n (%)	75 (39.9)
Type of cancer – n (%)	
Lung cancer	26 (13.8)
Hepatocellular carcinoma	9 (4.8)
Cholangiocarcinoma	49 (26.1)
Gynecologic cancer	35 (18.6)
Hematologic cancer (lymphoma and leukemia)	8 (4.3)
Other cancer	61 (32.4)

Continuous data are presented as median (interquartile range).

BMI=body mass index; CSMBS=civil servant medical benefits scheme; DVT=deep vein thrombosis; HRT=hormone replacement therapy; PE=pulmonary embolism; SSS=social security system; UC=universal coverage; VTE=venous thromboembolism

Dyspnea was the most common presentation of acute PE among all types of cancer. D-dimer level was numerically high in patients with CCA, hepatocellular carcinoma, and lung cancer who had acute PE. In-hospital PE was highly

prevalent in patients with gynecologic cancer and CCA.

The survival of patients was shown in Figure 1A. Among all patients with cancer-associated acute PE, the mean survival (95% confidence interval, CI) was 11.8 (8.3 to 15.3) months, (Figure 1A). The mean survival (95% CI) of patients with massive and non-massive acute PE were 6.5 (0.8 to 12.1) and 12.0 (8.4 to 15.7) months, respectively (p=0.289), (Figure 1B). Among the subgroups of cancer type, the mean survival (95% CI) in patients with lung cancer, hepatocellular carcinoma, CCA, gynecologic cancer, and hematologic cancer were 6.4 (2.5 to 10.3), 2.2 (0.0 to 4.5), 9.1 (3.9 to 14.4), 18.0 (7.7 to 28.3), and 1.3 (0.2 to 2.4) months, respectively, (p=0.007), (Figure 1C).

Discussion

From the present registry, the authors have demonstrated that cancer-associated acute PE was the most prevalent etiology of acute PE in this era (54.2% in the present report). Although any malignancies can be related with VTE, CCA was found to be the most prevalent form of cancer-associated with acute PE in the present study region (26.1%). The clinical presentation of acute PE in patients with cancer was similar to acute PE from other causes. Notably, many patients (39.9%) had acute PE as an in-hospital PE fashion. Parenteral medical treatment options, i.e., systemic thrombolysis and anticoagulants, were seemingly underused in this group of patients. Transcatheter treatment, either transcatheter embolectomy or transcatheter thrombolytic infusion, was performed in a small number of patients (2.7%), and surprisingly, no patient underwent surgical thromboembolectomy. A small number of patients developed major bleeding or fatal bleeding. The authors’ found that the survival of these patients was poor.

The authors’ recent findings were similar to a previous report from the authors’ center, where Reechaipichitkul et al.⁽¹⁴⁾ retrospectively reviewed hospitalized patients with acute PE for eight years (2002 to 2009) at Srinagarind Hospital and found that cancer was the dominant etiology of acute PE admission (62.1%). The authors reported CCA, gynecologic cancer, and lung cancer as the majority of associated cancers. Such a similarity might be attributed to a unique characteristic of CCA, the highest incidence of cancer in the Northeastern region of Thailand, and the highest in the world⁽¹⁵⁾. A recent study from the Northern region of Thailand found cancer as being the most common risk factor for acute PE (55.7%), in which lung cancer, CCA, and colorectal cancer were the majority⁽¹⁶⁾. Another recent study from the Central region of the country also reported cancer as being the most common risk factor of acute PE (46.1%)⁽¹⁷⁾. Considering the aforementioned reports from the Central region^(11,12), the authors could probably address that active cancer is the most common risk factor of acute

Table 2. Treatments and bleeding outcomes

Treatment and bleeding outcomes	All patients (n=188)	Subgroup massive PE (n=14)	Subgroup non-massive PE (n=174)	p-value
Systemic thrombolysis, n (%)				0.001
Alteplase	8 (4.3)	3 (21.4)	5 (2.9)	
Streptokinase	1 (0.5)	0	1 (0.6)	
Parenteral anticoagulant, n (%)				<0.001
UFH	56 (29.8)	10 (71.4)	46 (26.4)	
Enoxaparin	106 (56.4)	1 (7.1)	105 (60.3)	
Fondaparinux	0	0	0	
Oral anticoagulant, n (%)				0.267
Warfarin	65 (34.8)	2 (14.3)	63 (36.4)	
Apixaban	0	0	0	
Rivaroxaban	0	0	0	
Dabigatran	2 (1.1)	0	2 (1.2)	
Transcatheter thrombectomy, n (%)	3 (1.6)	2 (14.3)	1 (0.6)	0.015
Transcatheter thrombolytics infusion, n (%)	2 (1.1)	1 (7.1)	1 (0.6)	0.144
Surgical thromboembolectomy, n (%)	0	0	0	
IVC filter implantation, n (%)	3 (1.6)	1 (7.1)	2 (1.1)	0.208
Major bleeding, n (%)	12 (6.5)	1 (7.1)	11 (6.5)	>0.999
Fatal bleeding, n (%)	1 (0.5)	0	1 (0.6)	>0.999
Intracranial bleeding, n (%)	1 (0.5)	1 (7.1)	0	0.076

IVC=inferior vena cava; PE=pulmonary embolism; UFH=unfractionated heparin

PE across Thailand. Type of cancer, however, may be varied according to the local characteristics of the dwelling population.

The prevalence of in-hospital or incidental acute PE in the present study is relatively higher than a recent study conducted in the Northern part of Thailand (39.9% vs. 32.8%)⁽¹⁶⁾. The present study finding was in line with other findings around the globe, indicating the incidence of incidental acute PE is increasing. This could be an effect of increasing prevalence of cancer and improving the technology and more expertise of radiologists in detection of silent PE in patients with cancer who underwent computed tomography study for indication other than workup for PE⁽¹⁸⁾.

About one-fifth of patients were diagnosed with massive acute PE, but 4.8% of the patients in the present study received systemic thrombolysis, considered as a small number. Nevertheless, this was parallel with a recent study from Italy, where 3.4% of the patients in the group of acute PE and active cancer received thrombolysis, and 3.7% and 6.1% of patients in the group of acute PE with previous cancer and with no cancer received thrombolysis, respectively ($p=0.002$)⁽¹³⁾. The reason for such phenomenon could be a heterogeneity in contraindications of thrombolysis, which were reported in 18.8%, 9.1%, and 6.0% of patients in each group, respectively⁽¹³⁾. Although the authors were not able to demonstrate the contraindications of thrombolysis in our study, most patients with active cancer usually presented

with comorbidities or frailty, making most physicians tend to avoid systemic thrombolysis administration. Even though a large proportion of patients in the present study received parenteral anticoagulation (82.6%), it was not theoretically used in all patients with acute PE. This could be due to the frailty condition of the cancer patients. Due to an underuse of parenteral antithrombotic agents in the authors' practice, the rate of major bleeding and fatal bleeding were low.

During the present study period, direct oral anticoagulants (DOACs) were not yet recommended as a standard treatment for cancer-associated acute PE⁽¹⁹⁾, therefore warfarin was the main oral anticoagulant being used in patients who refrained from parenteral therapy. Interestingly, no patients underwent surgical revascularization for acute PE in the authors practice although 14 patients suffered from massive PE. This phenomenon could probably be explained from patients' frailty or poor conditioning from cancer. Regarding the transcatheter intervention, only 5 patients (2.7%) underwent percutaneous revascularization. The proportion was very low, partly because no dedicated device was available, and the expertise of physicians was insufficient at the time.

The survival of the patients was poor, similar to that in large global reports^(13,20-22). Interestingly, there was no statistical difference in the survival between patients with massive and non-massive acute PE in the present study, indicating that the degree of right ventricular dysfunction

Table 3. Characteristics, treatment, and bleeding outcomes according to type of cancer

Variables	Lung cancer (n=26)	Hepatocellular carcinoma (n=9)	Cholangiocarcinoma (n=49)	Gynecologic cancer (n=35)	Hematologic cancer (lymphoma + leukemia) (n=8)	Other cancers (n=61)
Age (years)	63 (24 to 84)	63 (50 to 71)	65 (42 to 81)	54 (32 to 87)	73.50 (44 to 81)	58 (18 to 87)
Female - n (%)	15 (57.7)	1 (11.1)	20 (40.8)	35 (100)	5 (62.5)	29 (47.5)
BMI (kg/m2)	20.1 (17.2 to 28.6)	25.3 (21.6 to 31.6)	21.9 (16.6 to 30.9)	24.0 (18.7 to 30.2)	24.8 (18.2 to 25.2)	22.8 (12.8 to 37.2)
Duration of symptom (hours)	72 (0.5 to 336)	240 (24 to 504)	120 (9 to 336)	192 (1 to 720)	108 (48 to 168)	72 (2 to 2,160)
Clinical presentation - n (%)						
Dyspnea	13 (56.5)	5 (55.6)	27 (58.7)	14 (43.8)	4 (57.1)	33 (60.0)
Chest pain	4 (18.2)	1 (11.1)	2 (4.9)	1 (3.6)	0	4 (8.3)
Syncope	0	0	0	0	0	2 (4.3)
Shock/hypotension	1 (4.3)	0	3 (7.0)	1 (3.3)	0	5 (10.0)
Cardiac arrest	2 (8.7)	0	2 (4.7)	0	0	7 (13.2)
Sign of DVT	9 (36.0)	2 (22.2)	14 (29.8)	12 (36.4)	1 (14.3)	9 (17.6)
D-dimer (mcg/L)	8,208 (1,522 to 38,777)	9,101 (285 to 16,529)	10,691 (2,670 to 31,260)	3,298 (640 to 17,546)	3,217 (2,327 to 5,219)	5,610.5 (816 to 40,441)
Classification of acute PE - n (%)						
Low risk	7 (26.9)	3 (33.3)	9 (18.4)	13 (37.1)	2 (25.0)	15 (24.6)
Sub-massive	17 (65.4)	6 (66.7)	37 (75.5)	21 (60.0)	6 (75.0)	38 (62.3)
Massive	2 (7.7)	0	3 (6.1)	1 (2.9)	0	8 (13.1)
In-hospital PE - n (%)	3 (11.5)	1 (11.1)	23 (46.9)	19 (54.3)	3 (37.5)	26 (42.6)
Treatment - n (%)						
Systemic thrombolysis	1 (3.8)	0	4 (8.2)	0	0	4 (6.7)
Parenteral anticoagulant	24 (92.3)	7 (77.8)	44 (89.8)	28 (80.0)	8 (100)	51 (83.6)
Oral anticoagulant	9 (34.6)	3 (33.3)	19 (38.8)	12 (34.3)	1 (12.5)	23 (38.3)
Transcatheter thrombectomy	0	0	0	0	0	3 (4.9)
Transcatheter thrombolytics infusion	0	0	0	0	0	2 (3.3)
Surgical thromboembolectomy	0	0	0	0	0	0
IVC filter implantation	0	0	0	0	0	3 (4.9)
Complication - n (%)						
Major bleeding	1 (4.0)	1 (11.1)	1 (2.0)	3 (9.1)	0	6 (10.0)
Fatal bleeding	0	0	0	0	0	1 (1.7)
Intracranial bleeding	0	0	0	0	0	1 (1.7)

Continuous data are presented as median (interquartile range).
BMI=body mass index; DVT=deep vein thrombosis; PE=pulmonary embolism; IVC=inferior vena cava

alone might not be able to determine the prognosis of acute PE like in general patients. The authors speculate that ailments from active cancer itself could play a major role in determining the prognosis of patients with cancer-associated acute PE, which this postulation was supported by findings from a recent COPE study⁽¹³⁾. However, the number of patients with massive PE in the present study was relatively small, limiting the authors from drawing a strong conclusion for this issue.

The present study contains some limitations. Importantly, this is a single center setting with a non-large population. Additionally, some characteristics such as clinical features of patients and pattern of treatment were

unique, therefore it was difficult to generalize the data or draw a firm conclusion. Although data acquisition was carefully done by training physicians, missing data was encountered as a nature of a retrospective study. Despite cancer being the major risk factor for acute PE in the present study, there were several other confounding risk factors for acute PE in the study patients, e.g., recent immobilization, recent surgery, or recent critical care admission. Hence, the clinical outcomes of acute PE in the present study might not be solely attributable to active cancer condition. Finally, the authors did not collect the metastatic status of cancer, by which recent studies have found metastatic cancer was prevalent and prognosticated a short survival^(13,22). However,

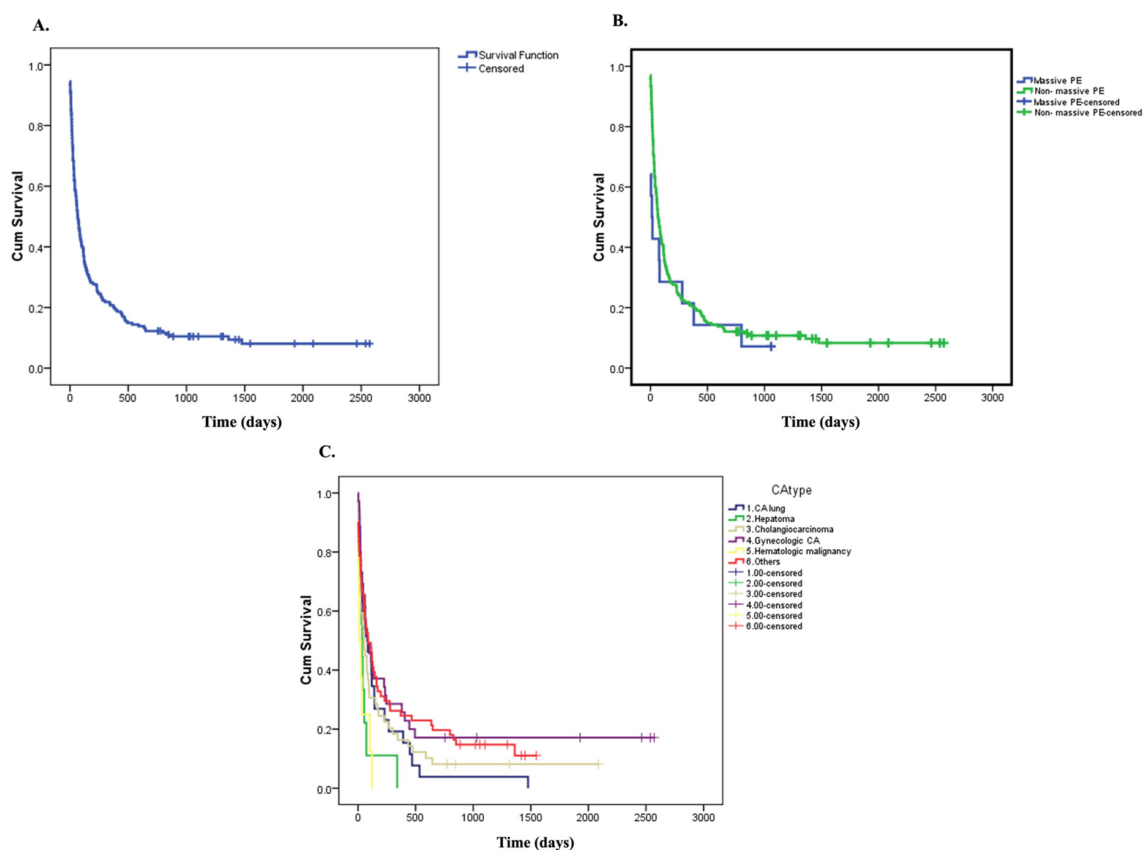


Figure 1. Kaplan-Meier plot of survival of patients with cancer-associated acute pulmonary embolism in all patients (A), between patients with massive versus non-massive acute pulmonary embolism ($p=0.289$) (B), and among subgroups of cancer ($p=0.007$) (C).

the present study has some strengths, as to the best of their knowledge, the present study is the largest study regarding the number of patients with cancer-associated acute PE in Thailand, and the survival of patients was extendedly followed for at least 2 years after admission.

Conclusion

Cancer is the most common risk factor for acute pulmonary embolism, and the most prevalent cancer type is cholangiocarcinoma in the Northeastern part of Thailand. Most patients with cancer-associated acute PE presented with sub-massive severity, and a sizable number of patients presented with in-hospital PE. Treatment was confined to parenteral anticoagulants, whereas systemic thrombolysis and surgical revascularization were underutilized. The prognosis of patients with cancer-associated acute PE was poor.

What is already known on this topic?

Cancer is the strongest risk factor for acute pulmonary embolism around the world.

Treatment of acute pulmonary embolism in patients with active cancer varies across the globe, depending on the characteristics of patients, availability of treatment options, and the expertise of physicians.

The survival of patients with acute pulmonary embolism who have active cancer is worse than patients who have no cancer.

What this study adds?

Cancer is the most common risk factor for acute pulmonary embolism in Thailand, and cholangiocarcinoma is the most prevalent cancer that is associated with acute pulmonary embolism in the Northeastern part of Thailand. Most patients with cancer-associated acute PE presented with sub-massive severity, and a sizable number of patients presented with in-hospital PE.

Revascularization, either thrombolysis or intervention, for patients with cancer-associated acute pulmonary embolism is seemingly underutilized, probably because of the prohibited conditions that are relevant to active cancer status.

The survival of patients with cancer-associated pulmonary embolism is poor, with an average survival of less than 1 year, and is not impacted by severity of pulmonary embolism.

Acknowledgements

The authors thank the Department of Internal Medicine, Faculty of Medicine, Khon Kaen University for publication support. The authors also thank Ms. Kaewjai Thepsuthammarat and Ms. Aroonsri Sanmuang for their assistance in statistical analyses.

Funding Resources

The present study received funding from invitation research grant of Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (IN59347).

Conflicts of interest

The authors declare no conflict of interest.

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