Clinical features and diagnosis of new malignancy in patients with acute pulmonary embolism and without a history of cancer

Yen-Chung Lin[a,b], Su-Chan Chen[c], Chi-Ming Huang[c], Yu-Feng Hu[c,d], Yun-Yu Chen[c,e], Shih-Lin Chang[c,d], Li-Wei Lo[c,d], Yenn-Jiang Lin[c,d,*], Shih-Ann Chen[c,d]

[a]Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan, ROC; [b]Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [c]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Institute of Clinical Medicine, and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, ROC; [e]Institute of Epidemiology and Preventive Medicine College of Public Health, National Taiwan University, Taipei, Taiwan, ROC

Abstract

Background: Pulmonary embolism (PE) is frequently associated with cancer. This study aimed to assess patients with acute PE and identify diagnostic predictors of new cancer after 1 year of follow-up.

Methods: One hundred and twenty-one patients with PE were enrolled consecutively from the emergency department of a single medical center in Taiwan. Data from computed tomography angiography, echocardiogram, electrocardiogram and for baseline comorbidities, clinical presentation, and laboratory parameters were recorded. The surviving discharged patients without a cancer diagnosis were followed-up for 1 year, and new malignancies were recorded.

Results: Of 121 patients with acute PE, 44 (36%) had an underlying cancer history (cancer group), and 77 (64%) did not (non-cancer group). Baseline demographic characteristics, comorbidities, clinical symptoms, biochemical parameters, echocardiogram data, and electrocardiogram data of the two groups were similar except for a higher hospital mortality rate (56.8% vs 9.1%; $p < 0.001$), lower body mass index (22.6 ± 4.1 vs 25.5 ± 4.9; $p = 0.02$), higher systolic blood pressure (139.7 ± 33.7 vs 125.4 ± 24.1; $p = 0.02$), lower low-density lipoprotein level (67.4 ± 38.3 vs 90.4 ± 33.8; $p = 0.04$), lower creatinine kinase (CK; 43.0 ± 43.0 vs 83.5 ± 83.1; $p = 0.01$), higher myocardial band (MB) form of CK ratio (0.2 ± 0.2 vs 0.1 ± 0.1; $p < 0.01$), higher partial pressure of arterial oxygen (122.81 ± 81.2 vs 90.2 ± 59.4; $p = 0.03$), and less presentation of chest pain (15.9% vs 40.3%; $p = 0.01$) in the cancer group. Kaplan–Meier curve analysis revealed that the 30-day survival rate was higher in the noncancer group than in the cancer group (log-rank $p = 0.04$). After 1 year of follow-up, 6 of 59 (10.17%) initial non–cancer-related PE survivors were diagnosed with malignancies. After multivariate analysis, only the initial CK-MB level was associated with a diagnosis of new cancer (hazard ratio [HR]: 1.37, 95% confidence interval [CI]: 1.029–1.811; $p = 0.03$).

Conclusion: This study suggests that the CK-MB level is associated with future malignancy in patients with PE. Patients with cancer-related PE had a worse 30-day survival rate.

Keywords: Computed tomography; Mortality; Pulmonary embolism

1. INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of mortality and morbidity among patients with cancer.[1] A history cancer is associated with a 2- to 8-fold increased risk of VTE.[2] VTE itself may be a sign of an occult malignancy (cancers of unknown primary).[3] Baron et al[4] found that the risk ratio was 4.4 for cancer after a diagnosis of VTE. The risk of recurrent VTE is greatest in the first few months after a malignancy is diagnosed. Hematologic malignancies and pancreatic cancer are the two most common types of tumors, which are associated with VTE. Earlier research suggests that the odds ratio for newly diagnosed malignancy in patients with VTE is three times higher than those without VTE.[5] Because VTE can be the first manifestation of an occult malignancy, investigation of the predictors of cancer in patients with VTE is warranted. In 2015, Carrier et al[6] reported a randomized clinical trial of 854 patients with VTE, 3.9% of them had newly diagnosed cancer after 1 year of follow-up, but routine computed tomography (CT) screening did not have a clinical benefit for early detection.

Among VTE, PE (a disease with a high in-hospital mortality rate of up to 10% in some reports) is one of the leading causes of death in hospitalized cancer patients.[7] Although risk stratification for PE is well documented,[8] predictors for cancer in patients with PE are not well studied. Early and noninvasive

*Address correspondence. Dr. Yenn-Jiang Lin, Division of Cardiology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: linyennjiang@gmail.com (Y.-J. Lin).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 245-250.

Received July 17, 2019; accepted November 22, 2019.

doi: 10.1097/JCMA.0000000000000259.

Copyright © 2020, the Chinese Medical Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

screening for cancer in idiopathic PE yielded acceptable sensitivity. However, the improvement of survival is so far unknown in these patients.[9] In a previous study, the relationship and immediate outcome of acute PE patients who did not receive surgical intervention were not clear in terms of occult malignancy as the first manifestation of acute PE.

This study aimed to (1) prospectively survey the occurrence of occult malignancy and predictors of diagnosis of new cancer in patients with acute PE, and (2) investigate the short-term outcome of nonparaneoplastic-related acute PE and paraneoplastic-related acute PE.

2. METHODS

2.1 Study population

The population of this study was a patient cohort who had an occurrence of PE, hospitalized in Taipei Veterans General Hospital, a tertiary transferal center in Taipei City, between December 1, 2004, and September 31, 2009. In total, 121 patients were included in the study. All of the patients and physicians were anonymized, and the need for informed consent was waived. Taipei Veterans General Hospital's institutional review board exempted this study from a full review. Patients presenting at the emergency department and diagnosed with PE via CT angiography (CTA) were screened consecutively. The severity of PE (massive, submassive, or low risk) was based on clinical findings, including blood pressure (BP), bradycardia, cardiac enzymes, and electrocardiogram (ECG)/echo. Patients ≥18 years objectively diagnosed with acute PE (of any degree) were eligible. On admission, both hemodynamically stable and unstable patients (who could be stabilized after the initial medical treatment) were enrolled in this study. The exclusion criteria were recent (previous 6 months) acute coronary syndrome, a significant septic condition, illness with a predicted 6-month mortality >50% (eg, terminal metastatic cancer, end-stage acquired immune deficiency syndrome, end-stage heart or renal failure with no plan for transplantation or hemodialysis therapy), or a do-not-resuscitate order with a clinical plan to not treat the patient for PE. Patients' comorbidities were recorded based on historical records and chart review. Laboratory parameters were collected on arrival to the emergency department including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), creatinine, sodium (Na), lactate dehydrogenase (LDH), troponin-I (Trop-I), creatinine kinase (CK), myocardial band (MB) form of creatinine kinase (CK-MB), D-dimer, and partial pressure of arterial oxygen (PaO_2).

2.2 Echocardiogram assessment in patients with PE

Transthoracic echocardiogram (TTE) was performed in all patients with high-risk PE, who were hemodynamically unstable and presenting shock, syncope, cardiac arrest, tachycardia (heart rate >100 beats per minute), or persistent sinus bradycardia (heart rate <40 beats per minute). TTE was also indicated for hemodynamically stable patients with evidence of right ventricular dysfunction or strain identified on CTA, or a new complete or incomplete right bundle branch block, or anteroseptal ST- or T-wave changes on electrocardiography. The decision to perform TTE was based on clinical presentations, PE burden, and imaging findings. TTE helps to stratify risk, guide further medical management, monitor the response to therapy, and give prognostic information for a subset of patients at increased risk for PE-related adverse events. All TTE examinations were performed with an HP SONOS 5500 Echocardiography Ultrasound System (HP/Philips, Amsterdam, the Netherlands). Specific TTE findings suggesting an increased risk of poor outcomes, and that could help to monitor the treatment response, were evaluated serially. High-risk features of PE were carefully evaluated, including impaired right ventricular function, interventricular septum bulging into the left ventricle (D-shaped septum), dilated proximal pulmonary arteries, increased severity of tricuspid regurgitation, elevated pulmonary artery pressure, the McConnell sign (a feature of acute massive PE presenting akinesia of the mid-free wall of the right ventricle (RV) and hypercontractility of the apex).

Further, the RV-to-left ventricle basal diameter ratio was measured; and the right ventricular systolic pressure (RVSP) was estimated from the tricuspid regurgitation peak velocity (TRV) using the Bernoulli equation. Peak TRV was measured by continuous-wave Doppler effect across the tricuspid valve. Multiple views were taken to obtain the optimal window—right ventricular inflow view, parasternal short axis view (PSAX), apical four-chamber view (A4C), subcostal view or a modified view between the PASX and A4C views, and parameters of left atrium diameter (LAD), right atrial enlargement (RAE), RVSP, left ventricular ejection fraction (LVEF), and inferior vena cava (IVC) diameter were recorded. Typical electrocardiogram (EKG) features for PE, such as ST-T change or S1Q3T3 (S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III) were also reviewed. Clinical presentation of chest pain or dyspnea was recorded. Patients were initially grouped into a cancer group and noncancer group based on medical records. Baseline characteristics, clinical and laboratory parameters, as well as significant hospital course events, were compared. Major hospital course events were considered as hemodynamic deterioration during hospitalization including a new onset of hemodynamic collapse, need for treatment upgrading (such as thrombolysis therapy, emergency surgical embolectomy, or catheter thrombus fragmentation), need for endotracheal intubation or cardiopulmonary resuscitation, systolic BP persistently <100 mmHg, refractory to volume loading, and requiring vasopressors treatment. The initially noncancer group was followed for 1 year or until diagnosed with cancer.

2.3 Patients follow-up

All patients were treated with warfarin (COUMADIN, Bristol-Myers Squibb Company, New York, NY) during the follow-up period and were under regular clinical follow-up at 15, 30, 60, and 90 days after discharge. Mortality was confirmed by searching the hospital's electronic medical records system. A staff assistant contacted the survivors by telephone 90 days after discharge. New-onset malignancy was confirmed via a medical records review by an independent staff 1 year after discharge.

2.4 Statistical analysis

Quantitative variables are expressed as the mean ± SD. A chi-square test with a Fisher's exact test was used for the categorical data. The normally distributed continuous variables were compared using the Student's *t* test, whereas the abnormally distributed variables were compared using a Mann-Whitney *U* test. Variables selected to be tested in the multivariate analysis were those with a p value <0.2 in the univariate models, to determine factors associated with new-onset of cancer in initially noncancer patients. Kaplan–Meier analysis was used to investigate the 30-day mortality among initial cancer and noncancer groups. P values <0.05 were considered to be significant. Statistical analysis was performed using the SPSS statistical package (version 17.0, Chicago, IL).

3. RESULTS

3.1 Clinical presentation, divided by cancer or noncancer patients

Table 1 summarizes demographic characteristics, baseline clinical parameters, biochemistries, and clinical parameters of the

Table 1

Baseline characteristics in patients with pulmonary embolism according to the status of cancer (n =121)

	Cancer group (n = 44)	Noncancer group (n = 77)	*p*
Median age (years)	69.3 ± 11.0	72.6 ± 16.0	0.22
Male gender (%)	26 (59.1)	49 (63.6)	0.70
Body mass index	22.6 ± 4.1	25.5 ± 4.9	0.02
Comorbidities			
Hypertension (%)	17 (38.6%)	42 (54.5%)	0.13
Hyperlipidemia (%)	2 (4.5%)	14 (18.2%)	0.05
Type 2 diabetes (%)	7 (15.9%)	17 (22.1%)	0.48
Coronary artery disease(%)	3 (6.8%)	17 (22.1%)	0.04
Congestive heart failure (%)	4 (9.1%)	14 (18.2%)	0.20
Recent surgery (%)	1 (2.3%)	9 (11.7%)	0.09
Deep vein thrombosis (%)	4 (9.1%)	8 (10.4%)	NS
Immobilization (%)	3 (6.8%)	5 (6.5%)	NS
Chronic renal failure (%)	17 (38.6%)	32 (41.5%)	0.70
Chronic obstructive pulmonary disease (%)	3 (6.8%)	14 (18.2%)	0.11
Vital signs			
Systolic blood pressure	139.7 ± 33.7	125.4 ± 24.1	0.02
Heart rate	105.4 ± 21.0	97.5 ± 18.6	0.05
Biochemistry data			
Cholesterol (mg/dL)	146.0 ± 69.0	155.9 ± 49.8	0.49
HDL-C (mg/dL)	29.6 ± 15.7	41.7 ± 17.0	0.05
LDL-C (mg/dL)	67.4 ± 38.3	90.4 ± 33.8	0.04
Creatinine (mg/dL)	1.2 ± 0.6	1.4 ± 0.8	0.11
Sodium (mEq/L)	137.2 ± 5.1	139.3 ± 5.4	0.05
LDH (mg/dL)	371.3 ± 191.3	342.7 ± 177.5	0.53
D-dimer (mg/dL)	11.8 ± 13.7	12.4 ± 28.4	0.91
CK (mg/dL)	43.0 ± 43.0	83.5 ± 83.1	0.01
CK-MB (mg/dL)	7.4 ± 8.5	4.8 ± 4.7	0.08
CK-MB/CK	0.2 ± 0.2	0.1 ± 0.1	<0.01
Troponin-I (mg/dL)	0.6 ± 1.3	0.8 ± 2.8	0.75
CRP (mg/dL)	5.6 ± 6.9	6.3 ± 8.0	0.69
Pao_2 (mmHg)	122.8 ± 81.2	90.2 ± 59.4	0.03
Echocardiography data			
LAD (mm)	37.4 ± 9.7	40.6 ± 8.7	0.29
RAE	4 (9.0%)	20 (26.0%)	0.03
RVSP (mmHg)	43.7 ± 17.0	48.4 ± 20.6	0.39
LVEF (mmHg)	47.8 ± 16.1	52.8 ± 11.0	0.19
IVC diameter (cm)	2.0 ± 0.3	5.0 ± 6.1	0.43
Clinical presentation			
Chest pain	7 (15.9%)	31 (40.3%)	0.01
Dyspnea	38 (86.4%)	63 (81.8%)	0.41
EKG presentations			
ST-T change	17 (38.6%)	20 (26.0%)	0.10
S1Q3T3	4 (9.0%)	18 (23.4%)	0.09
Severity			0.01
Massive	7 (15.9%)	21 (27.3%)	
Submassive	11 (24.4%)	32 (41.6%)	
Low risk	26 (57.8%)	24 (31.2%)	

Levels are marked with mean ± SD.

CK-MB = myocardial band form of creatinine kinase; CK = creatinine kinase; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; IVC = inferior vena cava; LAD = left atrium diameter; LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; Na = sodium; NS = not significant; Pao_2 = partial pressure of arterial oxygen; RAE = right atrial enlargement; RVSP = right ventricular systolic pressure; TC = total cholesterol.

study population (n = 121), cancer group (n = 44), and noncancer group (n = 77). Cancer and noncancer groups had comparable age and gender. With regard to comorbidities, the two groups had similar percentages of DVT, immobilization, and a recent history of surgery. On initial presentation, the groups had similar vital signs except as described hereafter. The cancer group had a significantly higher systolic BP (139.7 ± 33.7 vs 125.4 ± 24.1; p = 0.02), lower LDL-C level (67.4 ± 38.3 vs 90.4 ± 33.8; p = 0.04), lower CK level (43.0 ± 43.0 vs 83.5 ± 83.1; p = 0.01), higher CK-MB/CK ratio (0.2 ± 0.2 vs 0.1 ± 0.1; p = 0.003) higher Pao_2 (122.81 ± 81.2 vs 90.2 ± 59.4; p = 0.03), and less presentation of chest pain (15.9% vs 40.3%; p = 0.01). The ECG parameter and TTE parameters were similar between the two groups. The prevalence of RV strain and RVSP was comparable between the two groups.

3.2 Short-term survival between cancer and noncancer patients: Kaplan–Meier curve

Table 2 presents the mortality and major hospital events of the two groups. Cancer patients had a significant higher in-hospital

Table 2

Mortality and major hospital course events in patients with pulmonary embolism according to the status of cancer (n =121)

	Cancer group (n = 44) (%)	Noncancer group (n = 77) (%)	*p*
In-hospital mortality	25 (56.8)	7 (9.1)	<0.001
30-d mortality	10 (22.7)	7 (9.1)	0.06
Hospital courses			
Required mechanical ventilation	8 (18.2)	14 (18.2)	0.41
Occurrence of hemodynamic shock and inotropic agents	6 (13.6)	11 (14.3)	0.41

mortality (56.8% vs 9.1%, retrospectively; $p < 0.001$). Cancer patients tended to have a higher 30-day mortality rate (22.7% vs 9.1%, retrospectively; $p = 0.06$). In addition, the Kaplan–Meier survival estimate showed higher 30-day survival rate in the noncancer patients than in the cancer patients (Fig.; log-rank test; $p = 0.04$).

3.3 Predictor of occult malignancy patients

Among 77 patients without cancer at the time of presenting PE, 65 patients survived and were followed for 1 year. Six of 65 patients (9.23%) were diagnosed with cancer within 1 year of follow-up and 59 patients remained cancer-free. Table 3 shows the demographic differences between the new-onset of cancer (n = 6) from those who remained cancer-free during 1 year of follow-up (n = 59). The incidence of new-onset cancer was 9.23%, and those who had a new-onset cancer (n = 6) had a higher initial level of CK-MB (12.0 ± 10.1 vs 4.5 ± 4.1; $p < 0.01$), lower LVEF (36.0 ± 22.6 vs 53.6 ± 10.0; $p = 0.03$). After multivariate adjustment, including chest pain and dyspnea, initial CK-MB level was independently associated with a diagnosis of new cancer (Table 4, hazard ratio: 1.365, 95% confidence interval: 1.029–1.811; $p = 0.03$).

4. DISCUSSION

The main findings of this study are that compared with patients without underlying cancer history, those who had cancer when presenting acute PE had a higher CK-MB/CK ratio and worse short-term survival. In addition, the initial CK-MB level was significantly associated with a diagnosis of new cancer during the 1-year follow-up period, which could be considered as a novel predictor of cancer. The strength of this cohort was that there was a 100% follow-up rate at our hospital, resulting in the novel findings that a new onset of malignancy was associated with PE severity and cardiac biomarkers.

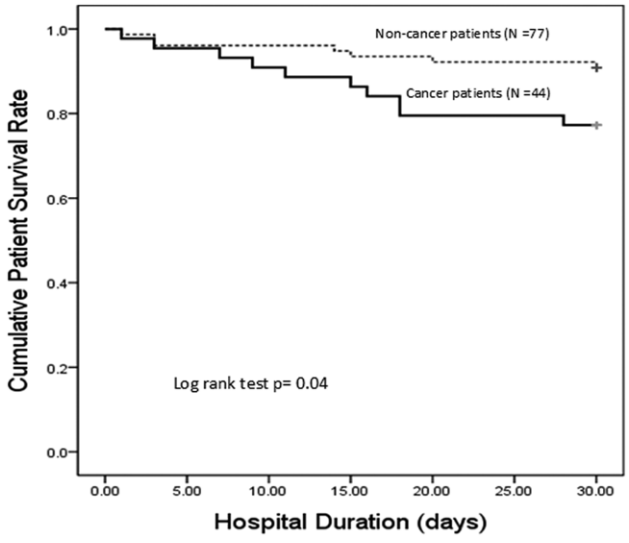

Fig. Kaplan–Meier curve of the study population (n = 121), divided by cancer (n = 44) or noncancer patients (n = 77).

The two groups (divided by being initially with or without cancer) had similar baseline characteristics. Several studies have examined the risk stratification of patients with PE. In a multicenter prospective study, the author reported N-terminal pro b-type natriuretic peptide as a useful marker for identifying low-risk PE.[10] On the other hand, predictors of unfavorable outcomes in PE include high PE severity index (PESI) containing variables of age, chronic cardiopulmonary disease, cancer, oxygenation, systolic BP, and heart rate.[11] In this study, cancer-related PE had worse short-term outcomes than the initial noncancer group despite a lower percentage of concurrent heart failure, higher systolic BP, and better oxygenation. However, CK-MB/CK ratio was higher in that group. CK-MB is the MB fraction of CK, mostly in the heart, which increases in the presence of acute ischemia. Cardiac enzymes, especially Trop-I, are often used for risk stratification in patients with PE. In a prospective cohort study of 318 stable patients with PE, Trop-I was a predictor of fatal events.[10] Other studies also showed that Trop-I and hypoxemia were associated with in-hospital mortality.[11] The consequence of more severe PE represents massive pulmonary embolism in image examinations, and is related to decompensated cardiopulmonary reserve and cardiomyocyte damage reflected by an elevation of cardiac enzymes.[9] Although Trop-I was elevated in 50% of PE cases, CK-MB elevation was only observed in 26.5% PE events.[12] CK-MB is one of the various cardiac enzymes and elevation may represent cardiomyocyte damage leading to worse short-term survival.

The exact explanation for why CK-MB was significantly associated with the diagnosis of new cancer after 1 year is unclear, but it could be partially attributed to PE severity. CK-MB is also elevated in various noncardiac conditions such as renal failure.[13] In earlier research, chronic kidney disease was also increased with the incidence of PE in patients with breast cancer.[14] Another explanation is the phenomenon of ectopic production of CK-MB in patients with various cancers, which is well documented in the literature.[15–17] There was also a case report showing that CK-MB may be falsely elevated in the presence of cancer-related macromolecules.[18] The incidence of occult cancer after PE in our study was 9.23%, which was comparable to the report in other cohorts of DVT (2.7%–26.3%).[5]

Screening for occult cancer in idiopathic VTE had been a contentious debate. Significant evidence establishes a close relationship between VTE and malignancy.[19] An estimated 20% of idiopathic pulmonary thromboembolism patients had an occurrence of new cancer 1 year after the venous thrombotic event, which was significantly higher than a previous study.[20] Clinicians need to understand how extensively they should screen for cancer. Limited screening for occult malignancy in these patients is performed in clinical practice. The most recent randomized controlled trial by Carrier et al[6] suggested that an additional CT

Table 3

Baseline characteristics and clinical parameters of new-onset of cancer (n = 6) and remain noncancer status in a 12-mo period (n = 59) in initially noncancer survivors with pulmonary embolism (n = 65)

	New onset of cancer (n = 6)	Remain noncancer status (n = 59)	*p*
Age (years)	77.2 ± 8.7	72.3 ± 16.5	0.47
Coronary artery disease	0 (0.0%)	16 (22.5%)	0.33
Type 2 diabetes	0 (0.0%)	17 (23.9%)	0.33
Chronic kidney disease	1 (1.7%)	31 (43.6%)	0.38
Chest pain	4 (66.7%)	18 (25.7%)	0.06
Dyspnea	3 (50.0%)	60 (84.5%)	0.06
Deep vein thrombosis	1 (16.7%)	21 (29.6%)	0.51
Serum creatinine (mg/dL)	1.5 ± 1.3	1.4 ± 0.8	0.86
CRP (mg/dL)	2.4 ± 0.2	6.4 ± 8.2	0.40
Pao_2 (mmHg)	91.4 ± 31.2	90.1 ± 61.0	0.97
CK (mg/dL)	147.5 ± 212.6	70.5 ± 70.0	0.11
CK-MB (mg/dL)	12.0 ± 10.1	4.5 ± 4.1	<0.01
Body mass index (kg/m^2)	21.8 ± 4.2	25.7 ± 4.8	0.18
Congestive heart failure	1 (16.7%)	13 (18.3%)	NS
LVEF (%)	36.0 ± 22.6	53.6 ± 10.0	0.03
Systolic BP (mmHg)	125.2 ± 45.0	125.4 ± 22.2	0.98

Levels are marked with mean ± SD.

BP = blood pressure; CK-MB = myocardial band form of creatinine kinase; CK =creatinine kinase; CRP = C-reactive protein; LVEF = left ventricular ejection fraction; NS = not significant; Pao_2 = partial pressure of arterial oxygen.

Table 4

Logistical regression model of factors associated with new-onset cancer disease in initially noncancer patients with pulmonary embolism (n = 65)

	Univariate			Multivariate[a]		
	HR	95% CI	*p*	HR	95% CI	*p*
Dyspnea (odd for nondyspnea = 1.0)	1.124	1.057–1.194	<0.01	…	…	…
CK-MB levels	1.265	1.026–1.561	0.03	1.365	1.029–1.811	0.03
Chest pain (odd for nonchest pain = 1.0)	0.173	0.029–1.026	0.05	…	…	…

CI = confidence interval; CK-MB = myocardial band form of creatinine kinase; HR = hazard ratio.

[a]Independent variables were selected for multivariate analysis if they had a *p* value <0.05 in the univariate analysis.

scan was not better than a limited screening strategy. If clinicians can identify the high-risk factors for the occult malignancy population in idiopathic VTE patients, then intensive screening for cancer will be of clinical usefulness. A study showed that cancer was associated with the location of DVT but not with PE. Jara-Palomares et al[9] suggested a shock index ≥1 and idiopathic PE were risk factors of occult cancer with PE. In our study, we found that the CK-MB level was significantly associated with a new cancer diagnosis during 1 year of follow-up. This study's findings may be helpful for physicians' future decision-making processes.

The strength of our study was that the diagnosis of PE was very robust, and all made by CTA (the gold-standard diagnosis tool for PE), with prospective, regular outpatient department follow-up for 1 year. Some limitations are notable, however. First, the number of patients diagnosed with cancer during 1-year follow-ups was few, which should be confirmed in larger populations. Second, the diagnosis of new cancer during the 1-year follow-up was performed by a medical chart review without a protocol for cancer screening. However, the incidence of newly diagnosed cancer was 9.23% which concurs with other research.[5]

We observed a high incidence of occult malignancy (9.3%) in patients with an initial manifestation of acute PE. A higher CK-MB level predicted the diagnosis of a new malignancy in patients with PE. Paraneoplasm-related acute PE (including prior diagnosis and occult cancer) was associated with a short-term survival rate in patients who did not initially undergo immediate intervention.

ACKNOWLEDGMENTS

This study was supported by the Ministry of Science and Technology of Taiwan support for the National Yang-Ming University and Taipei Veterans General Hospital (MOST 107-2314-B-010-061-MY2, MOST 106-2314-B-010-046-MY3); Grant of Taipei Veterans General Hospital (V108C-032, C17-095); Taipei Medical University Hospital Evidenced Based Medicine-Research Teaching (TMIUH-EBM-RT).

REFERENCES

1. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;**5**:632–4.
2. Lee AY. Screening for occult cancer in patients with idiopathic venous thromboembolism: no. *J Thromb Haemost* 2003;**1**:2273–4.
3. Bura A, Cailleux N, Bienvenu B, Léger P, Bissery A, Boccalon H, et al. Incidence and prognosis of cancer associated with bilateral venous thrombosis: a prospective study of 103 patients. *J Thromb Haemost* 2004;**2**:441–4.
4. Baron JA, Gridley G, Weiderpass E, Nyrén O, Linet M. Venous thromboembolism and cancer. *Lancet* 1998;**351**:1077–80.
5. Prins MH, Hettiarachchi RJ, Lensing AW, Hirsh J. Newly diagnosed malignancy in patients with venous thromboembolism. Search or wait and see? *Thromb Haemost* 1997;**78**:121–5.
6. Carrier M, Lazo-Langner A, Shivakumar S, Tagalakis V, Zarychanski R, Solymoss S, et al; SOME Investigators. Screening for occult cancer in unprovoked venous thromboembolism. *N Engl J Med* 2015;**373**:697–704.

7. Kakkar AK, Levine M, Pinedo HM, Wolff R, Wong J. Venous thrombosis in cancer patients: insights from the FRONTLINE survey. *Oncologist* 2003;**8**:381–8.
8. Huang CM, Lin YC, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Risk stratification and clinical outcomes in patients with acute pulmonary embolism. *Clin Biochem* 2011;**44**:1110–5.
9. Jara-Palomares L, Rodríguez-Matute C, Elías-Hernández T, Rodríguez-Portal JA, López-Campos JL, Garcia-Ibarra H, et al. Testing for occult cancer in patients with pulmonary embolism: results from a screening program and a two-year follow-up survey. *Thromb Res* 2010;**125**:29–33.
10. Jiménez D, Díaz G, Molina J, Martí D, Del Rey J, García-Rull S, et al. Troponin I and risk stratification of patients with acute nonmassive pulmonary embolism. *Eur Respir J* 2008;**31**:847–53.
11. Bova C, Pesavento R, Marchiori A, Palla A, Enea I, Pengo V, et al.; TELESIO Study Group. Risk stratification and outcomes in hemodynamically stable patients with acute pulmonary embolism: a prospective, multicentre, cohort study with three months of follow-up. *J Thromb Haemost* 2009;**7**:938–44.
12. Pruszczyk P, Bochowicz A, Torbicki A, Szulc M, Kurzyna M, Fijałkowska A, et al. Cardiac troponin T monitoring identifies high-risk group of normotensive patients with acute pulmonary embolism. *Chest* 2003;**123**:1947–52.
13. Haller C, Zehelein J, Remppis A, Müller-Bardorff M, Katus HA. Cardiac troponin T in patients with end-stage renal disease: absence of expression in truncal skeletal muscle. *Clin Chem* 1998;**44**:930–8.
14. Lin HF, Liao KF, Chang CM, Lin CL, Lai SW, Hsu CY. Correlation of the tamoxifen use with the increased risk of deep vein thrombosis and pulmonary embolism in elderly women with breast cancer: a case-control study. *Medicine (Baltimore)* 2018;**97**:e12842.
15. Lee BI, Bach PM, Horton JD, Hickey TM, Davis WA. Elevated CK-MB and CK-BB in serum and tumor homogenate of a patient with lung cancer. *Clin Cardiol* 1985;**8**:233–6.
16. Wu AH, Feng YJ, Nadelman J, Acampora M, Fiedler PN. Ectopic production of creatine kinase MB: updated evaluation by mass assays. *Clin Chem* 1997;**43**:2006–7.
17. Annesley TM, McKenna BJ. Ectopic creatine kinase MB production in metastatic cancer. *Am J Clin Pathol* 1983;**79**:255–9.
18. Kim S, Um TH, Cho CR, Jeon JS. False-positive elevation of creatine kinase MB mass concentrations caused by macromolecules in a patient who underwent nephrectomy for renal cell carcinoma. *Ann Lab Med* 2014;**34**:405–7.
19. Khorana AA. Cancer and thrombosis: implications of published guidelines for clinical practice. *Ann Oncol* 2009;**20**:1619–30.
20. Chen LK, Yen DH, Hsu PS, Chen TW, Hwang SJ. Acute pulmonary thromboembolism and occult cancer. *Zhonghua Yi Xue Za Zhi (Taipei)* 2002;**65**:106–10.