Original Article

Pulmonary embolism concurrent with lung cancer and central emboli predict mortality in patients with lung cancer and pulmonary embolism

Seung-Ick Cha[1], Kyung-Min Shin[2], Jae-Kwang Lim[2], Seung-Soo Yoo[1], Shin-Yup Lee[1], Jaehee Lee[1], Chang-Ho Kim[1], Jae-Yong Park[1], Won-Kee Lee[3], Chi-Young Jung[4]

[1]Department of Internal Medicine, [2]Department of Radiology, [3]Department of Preventive Medicine, Kyungpook National University School of Medicine, Daegu, Korea; [4]Department of Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, Korea

Contributions: (I) Conception and design: SI Cha, CY Jung; (II) Administrative support: SI Cha; (III) Provision of study materials or patients: SI Cha, KM Shin, JK Lim; (IV) Collection and assembly of data: SI Cha, SY Lee, SS Yoo; (V) Data analysis and interpretation: SI Cha, WK Lee; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Seung-Ick Cha, MD. Department of Internal Medicine, Kyungpook National University Hospital, 130 Dongdeok-ro, Jung-gu, Daegu 41944, Korea. Email: sicha@knu.ac.kr.

Background: Patients with lung cancer commonly experience pulmonary embolism (PE). The aim of the present study was to examine the clinical features of patients with lung cancer and PE and to investigate prognostic factors in these patients.

Methods: This retrospective study divided patients with lung cancer and PE into a group of patients with PE diagnosed concomitantly with lung cancer (concurrent group) and a group with PE detected after lung cancer (sequential group), compared the clinical characteristics of patients in the two groups, and investigated prognostic factors in these patients.

Results: The study population consisted of the concurrent group [27 patients (10.1%)] and the sequential group [240 patients (89.9%)]. The concurrent group exhibited higher percentages of stage I cancer at the diagnosis of PE [6 (22.2%) *vs.* 8 (3.3%), P<0.001] and right ventricular (RV) dilation on computed tomography (CT) [14 (51.9%) *vs.* 41 (17.1%), P<0.001], as well as lower rate of small cell carcinoma [1 (3.7%) *vs.* 49 (20.4%), P=0.036] than the sequential group. PE concurrent with lung cancer [hazard ratio (HR) =2.64, 95% confidence interval (CI): 1.57–4.43, P<0.001] and central PE (HR =1.46, 95% CI: 1.02–2.10, P=0.04) were independent predictors of mortality in patients with lung cancer and PE.

Conclusions: PE concurrent with lung cancer is characterized by more severe PE and infrequent small cell carcinoma. PE concurrent with lung cancer and central emboli may be independent prognostic factors in patients with lung cancer and PE.

Keywords: Computed tomography (CT); lung cancer; prognosis; pulmonary embolism (PE); venous thromboembolism (VTE)

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Introduction

Cancer is one of the important risk factors for venous thromboembolism (VTE). VTE occurs two to four times more frequently in patients with cancer than in those without cancer (1,2). In a study using a Medicare database, malignancies with the highest risk of VTE when adjusted for prevalence included ovarian cancer, brain tumors, and pancreatic cancer (3), whereas in a Dutch population-based study, hematologic malignancies were associated with the highest risk of VTE, followed by lung and gastrointestinal

cancers (4). Lung cancer is the most commonly identified malignancy in patients with VTE (5), with an incidence of 3–13.9% in patients with VTE and that of up to 3.8% in patients with pulmonary embolism (PE) (6-9).

The mechanisms of VTE in cancer patients, although not completely established, appear to be multifactorial (6,7). The occurrence of VTE in lung cancer has a prognostic implication, in that the survival of lung cancer patients with PE was shorter than that of those without PE (10). However, most deaths in patients with lung cancer and PE or VTE have been attributed to lung cancer rather than thromboembolism (11). These findings suggest that VTE may be a marker of an advanced stage cancer or of a more biologically aggressive tumor (12). A previous study including small numbers of patients demonstrated that patients with lung cancer with concurrently diagnosed PE had poorer survival than those without PE (10). In another study, no difference in survival was found between patients with PE diagnosed at less than 3 months after the diagnosis of lung cancer and those with PE diagnosed at 3 months or more following lung cancer diagnosis (13). Therefore, it is unclear whether the timing of the presentation of PE in patients with lung cancer may influence patient prognosis. Several factors that may determine short-term prognosis in patients with PE, including pulmonary embolism severity index (PESI) score, cardiac biomarkers, right ventricular (RV) dilation, and central emboli, have been proposed (14). However, information regarding these PE-related prognostic factors in patients with lung cancer and PE is lacking. The aim of the present study was to examine the clinical features of patients with lung cancer patients and PE, to compare clinical characteristics of PE found concurrently at lung cancer diagnosis and PE developed sequentially after the diagnosis of lung cancer, and to investigate the PE-related predictors of mortality in patients with lung cancer patients and PE.

Methods

Study design

The present study was retrospectively conducted at two university-affiliated hospitals [Kyungpook National University Hospital (KNUH) and Kyungpook National University Medical Center (KNUMC)] in Daegu, Korea. Patients with active lung cancer with PE, which had been diagnosed by computed tomography (CT), were enrolled. Active lung cancer was defined based on fulfillment of one of the following conditions: (I) detection of lung cancer within 6 months after PE diagnosis; (II) current therapy of supportive care or active anticancer treatment for lung cancer; (III) within 6 months after the end of anticancer therapy for lung cancer. The patients with lung cancer and PE were categorized into a group of patients with PE diagnosed concomitantly with lung cancer (concurrent group) and a group with PE detected after the diagnosis of lung cancer (sequential group). To identify patients with lung cancer patients and PE, we reviewed the database of patients with PE (14), searched electronic medical records under the diagnosis codes, and performed a search of CT readings of the two hospitals with the search terms of "lung cancer" and "pulmonary embolism" or "pulmonary thromboembolism" from January 2005 through December 2014 at KNUH and from January 2011 through December 2014 at KNUMC. Exclusion criteria were the following: (I) *in situ* pulmonary artery thrombosis (15); (II) pulmonary artery obstruction by tumor mass (tumor emboli); (III) lack of medical records; (IV) lack of available CT with interpretable quality images. This study was approved by the Institutional Review Board of each hospital (KNUH IRB 2016-09-020 and KNUMC 2016-10-005), which waived the requirement for written informed consent because of the retrospective nature of the study.

Data collection

Demographic data, symptoms, comorbid conditions, and risk factors for VTE were reviewed. PE was determined as unprovoked when no reversible provoking risk factors, such as surgery, trauma, pregnancy and puerperium within 3 months of the event, or immobilization (bed rest within the previous month for most of the day for ≥3 consecutive days) existed (16). The PESI score was retrospectively calculated (17). PE-related outcomes, including a PE-related in-hospital mortality, adverse outcomes, and VTE recurrence were assessed. An adverse outcome comprised PE-related in-hospital death and serious clinical conditions due to PE, including requirement for inotropic support, impending respiratory failure or mechanical ventilation, cardiopulmonary resuscitation, and secondary thrombolysis (18). A PE-related in-hospital death was defined if an in-hospital death was directly caused by PE, or if it could not be attributed to other causes and PE could not be excluded (18). Blood laboratory data, including serum N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and plasma troponin I, were also assessed.

Lung cancer-related data, including time between the diagnosis of lung cancer and PE detection, histologic type,

initial stage, stage at the diagnosis of PE, chemotherapy, and survival data, were reviewed. The stage of lung cancer was determined as stage I, II, III, or IV according to the seventh edition of the TNM classification developed by the International Association for the Study of Lung Cancer in 2009 (19), and pathologic stage was adopted in patients who underwent surgical resection.

Radiological evaluation

The diagnosis of PE was made on CT images as a sharply delineated pulmonary arterial filling defect in at least two consecutive sections, either located centrally within the vessel or with acute angles at its interface with the vessel wall (20). The largest pulmonary arteries in which pulmonary emboli were located were determined, and central PE comprised the right or left pulmonary artery or a more proximal location. The diameters of the RV and left ventricular (LV) were measured at their widest points between the inner surface of the free wall and the surface of the interventricular septum (21), and the RV/LV diameter ratios were calculated. An RV/LV diameter ratio of ≥1 was designated as RV dilation (18). Pulmonary infarction was defined as a peripheral consolidation in the region of pulmonary emboli, based on the modified criteria of a previous study (22).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). P values <0.05 were considered statistically significant. Data were expressed as means ± standard deviations (SDs) or medians [interquartile ranges (IQRs)] for non-normally distributed continuous variables and as numbers and percentages for categorical variables. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test if non-normally distributed, whereas categorical variables were compared using the Chi-squared test or Fisher's exact test. Survival was analyzed using the Kaplan-Meier method. Independent prognostic factors for survival were determined using a Cox proportional hazards model.

Results

Clinical characteristics with regard to PE

Overall, 5,005 patients with lung cancer were identified, and 267 patients with lung cancer and PE (5.3%) were included in the present study. Baseline characteristics of the patients are presented in *Table 1*. Patients' median age at the diagnosis of PE was 69 years (IQR, 63–84 years), and there was a higher proportion with men (65.2%). The most common risk factor for VTE, other than lung cancer, was chemotherapy [177 patients (66.3%)], followed by immobilization [14 patients (5.2%)]. Unsuspected PE was found in more than half (53.6%) of the patients. Most patients [220 (82.4%)] underwent anticoagulation therapy, and the reasons for lack of anticoagulation therapy were as follows: pulmonary emboli overlooked by attending physicians, n=19 (40.4%); contraindications to anticoagulation, n=3 (6.4%); refusal to receive anticoagulation, n=3 (6.4%); and unknown causes, n=22 (46.8%). PE-related in-hospital deaths, adverse outcomes, and recurrent VTE occurred in 2 (0.7%), 8 (3.0%), and 12 patients (4.5%), respectively. On CT scan, 48 patients (18.0%) had central PE, and RV dilation was noted in 55 patients (20.6%). Pulmonary infarction was observed in 18 patients (6.7%), and pleural effusion in 39 (14.6%).

Clinical characteristics with regard to lung cancer

Data concerning lung cancer are detailed in *Table 2*. The median time between the diagnosis of lung cancer and the detection of PE was 135 days (range, 69–320 days). PE developed before or at the time of diagnosis of lung cancer in 27 patients (concurrent group, 10.1%), and in the remaining patients, PE occurred after the diagnosis of lung cancer (sequential group). The most common histologic type of lung cancer was adenocarcinoma [140 (52.4%)], followed by squamous cell carcinoma [53 (19.9%)] and small cell carcinoma [50 (18.7%)]. When lung cancer was diagnosed, most patients (85.0%) had stage IV [160 (59.9%)] or III [67 (25.1%)] cancer. The median survival after the diagnosis of lung cancer was 448 days (range, 255–774 days) and the median survival after the diagnosis of PE was 207 days (range, 88–485 days). Of the 129 patients whose causes of death were identified, progression of lung cancer [121 (93.8%)] was the most common.

Comparisons between the concurrent and sequential groups

As noted above, all patients were categorized into either the concurrent or sequential group, and clinical parameters were compared between the two groups (*Table 3*). In the concurrent group, risk factors for VTE

Table 1 Clinical characteristics of the patients with regard to PE (n=267)

Characteristics	Values
Age at the diagnosis of PE (years)	69 [63–84]
Male sex	174 (65.2)
Ever-smoker	167 (62.5)
Body mass index (kg/m^2)	23±2.9
Risk factor for VTE	
Chemotherapy	177 (66.3)
Immobilization	14 (5.2)
Surgery or trauma	3 (1.1)
Previous VTE	4 (1.5)
Comorbid condition	
Hypertension	41 (15.4)
Diabetes mellitus	38 (14.2)
Chronic lung disease*	25 (9.4)
Respiratory tract infection	11 (4.1)
Ischemic heart disease	10 (3.7)
Congestive heart failure	8 (3.0)
Atrial fibrillation	8 (3.0)
Stroke	7 (2.6)
TB or NTM lung infection	4 (1.5)
Chronic liver disease	4 (1.5)
Hemoptysis	5 (1.9)
Pleuritic pain	9 (3.4)
Unsuspected PE	143 (53.6)
PESI	107 [99–118]
PESI class IV–V	151 (56.6)
DVT	55/78 (70.5)
Anticoagulation	220 (82.4)
Systemic thrombolysis	5 (1.9)
Vena cava filter placement	4 (1.5)
VTE recurrence	12 (4.5)
Adverse outcome	8 (3.0)
In-hospital death	20 (7.5)
PE-related in-hospital death	2 (0.7)
CT findings	
Central PE#	48 (18.0)
RV dilation	55 (20.6)
Pulmonary infarction	18 (6.7)
Pleural effusion	39 (14.6)
Blood biomarkers	
NT-proBNP (pg/mL) (n=143)	217 [79–517]
Troponin I (ng/mL) (n=150)	0.033 [0.015–0.060]

Data are presented as mean ± SD, median [IQR] or n (%). *, chronic lung disease includes chronic obstructive pulmonary disease, asthma, bronchiectasis, idiopathic pulmonary fibrosis, pneumoconiosis, and tuberculosis-destroyed lung; #, central pulmonary arteries mean the right or left pulmonary artery or a more proximal location. PE, pulmonary embolism; VTE, venous thromboembolism; TB, tuberculosis; NTM, nontuberculous mycobacteria; PESI, pulmonary embolism severity index; DVT, deep vein thrombosis; CT, computed tomography; RV, right ventricle; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; SD, standard deviation; IQR, interquartile range.

including immobilization [4 (14.8%) *vs.* 10 (4.2%), P=0.042], surgery/trauma [2 (7.4%) *vs.* 1 (0.4%), P=0.028], and previous VTE [2 (7.4%) *vs.* 2 (0.8%), P=0.052] were more common than in the sequential group, whereas chemotherapy was administered in 177 (73.8%) of the patients in the sequential group. Of the 50 patients with small cell carcinoma, PE developed sequentially after the diagnosis of lung cancer in 49 patients, of whom 45 underwent chemotherapy, with the other one having a predisposing condition of immobilization. RV dilation was significantly more common in the concurrent group [14 (51.9%) *vs.* 41 (17.1%), P<0.001] than in the sequential group, whereas the frequency of central PE was not significantly different between the two groups (*Table 4*). Systemic thrombolysis [2 (7.4%) *vs.* 3 (1.3%), P=0.081] and vena cava filter placement [3 (11.1%) *vs.* 1 (0.4%), P=0.003] were also more commonly performed in the concurrent group than in the sequential group. The median survival after the diagnosis of lung cancer was significantly shorter in the concurrent group than in the sequential group [214 (IQR, 19–409) *vs.* 498 (IQR, 430–566) days, P<0.001].

Table 2 Characteristics of lung cancer (n=267)

Characteristics	Values
Age at diagnosis of lung cancer	68 [62–73]
Time interval from the diagnosis of lung cancer to PE (days)	135 [69–320]
Lung cancer concurrent with PE	27 (10.1)
Lung cancer followed by PE	240 (89.9)
Histology of lung cancer	
Adenocarcinoma	140 (52.4)
Squamous cell carcinoma	53 (19.9)
Small cell carcinoma	50 (18.7)
Large cell carcinoma	6 (2.2)
Non-small cell carcinoma, not otherwise specified*	18 (6.7)
Initial stage of lung cancer	
I	24 (9.0)
II	16 (6.0)
III	67 (25.1)
IV	160 (59.9)
Stage of lung cancer at the diagnosis of PE	
I	14 (5.2)
II	11 (4.1)
III	59 (22.1)
IV	183 (68.5)
Survival after the diagnosis of lung cancer (days)	448 [255–774]
Survival after the diagnosis of PE (days)	207 [88–485]
Cause of death (n=244)	
Progression of lung cancer	121 (49.6)
PE-related death	4 (1.6)
Anticoagulation-related death	4 (1.6)
Unknown	115 (47.1)

Data are presented as median [IQR] or n (%). *, this histology includes unspecified non-small cell carcinoma (n=15), Adenosquamous cell carcinoma (n=1), sarcomatoid carcinoma (n=1), and adenocarcinoma combined with large cell carcinoma (n=1). PE, pulmonary embolism; IQR, interquartile range.

Survival analysis according to PE-related factors

Concurrence of lung cancer and PE (concurrent group *vs.* sequential group), presence *vs.* absence of anticoagulation, unsuspected *vs.* suspected PE, high PESI score (class IV–V *vs.* class I–III), central PE, and RV dilation were chosen as candidate PE-related prognostic factors that could affect the survival of patients with lung cancer (*Figure 1*). When adjusted for age, gender, smoking status (ever-smoker *vs.* never-smoker), stage (I–IV), and histologic type (small cell lung cancer *vs.* non-small cell lung cancer), concurrence of lung cancer and PE [hazard ratio (HR) =2.64, 95% confidence interval (CI): 1.57–4.43, P<0.001] and central PE (HR =1.46, 95% CI: 1.02–2.10, P=0.04) independently influenced the survival of patients with lung cancer and PE.

Discussion

The present study demonstrated that in patients with lung cancer and PE, the most common predisposing factors for PE after lung cancer alone was chemotherapy. The median time from the diagnosis of lung cancer to PE was 4.5 months, and approximately 10% of patients developed PE concurrently with lung cancer. The concurrent group was characterized by more common association with risk factors for VTE (immobilization, surgery or trauma and previous VTE), stage I lung cancer, and RV dilation than the sequential group. Nearly all patients with small cell lung cancer developed PE sequentially to lung cancer rather than concurrently. Of the PE-related parameters, concurrent diagnosis of PE in lung cancer and central PE were independent predictors of death in patients with lung cancer and PE, suggesting the timing of PE presentation and the size of emboli were important factors determining prognosis in these patients.

The most important clinical factors determining the rates of VTE in patients with lung cancer are stage and tumor histology (6). As expected, in the present study, most patients had advanced stage lung cancer. A hypercoagulable state in cancer has been commonly attributed to the production of mucin and overexpression of tissue factor (23). Mucin-producing adenocarcinomas of the lung are associated with increased risk of VTE (12). This finding can be explained by the concept that mucin may cause

Table 3 Comparisons of clinical characteristics between concurrent and sequential groups

Parameters	Concurrent (n=27)	Sequential (n=240)	P
Age at diagnosis of lung cancer (years)	68 [54–76]	68 [62–73]	0.621
Age at PE diagnosis (years)	68 [54–76]	69 [63–73]	0.972
Female gender	15 (55.6)	78 (32.5)	0.017
Ever-smoker	13 (48.1)	154 (65.0)	0.086
Body mass index (kg/m^2)	22±2.4	23±2.9	0.015
Risk factor for VTE			
Chemotherapy	0 (0.0)	177 (73.8)	<0.001
Immobilization	4 (14.8)	10 (4.2)	0.042
Surgery or trauma	2 (7.4)	1 (0.4)	0.028
Previous VTE	2 (7.4)	2 (0.8)	0.052
Comorbid condition			
Hypertension	3 (11.1)	38 (15.8)	0.778
Diabetes mellitus	3 (11.1)	35 (14.6)	0.777
Chronic lung disease*	1 (3.7)	24 (10.0)	0.487
Respiratory tract infection	0 (0.0)	11 (4.6)	0.610
Ischemic heart disease	1 (3.7)	9 (3.8)	>0.999
Congestive heart failure	0 (0.0)	8 (3.3)	>0.999
Atrial fibrillation	0 (0.0)	8 (3.3)	>0.999
Stroke	2 (7.4)	5 (2.1)	0.151
TB or NTM lung infection	0 (0.0)	4 (1.7)	>0.999
Chronic liver disease	0 (0.0)	4 (1.7)	>0.999
Hemoptysis	1 (3.7)	4 (1.7)	0.416
Pleuritic pain	3 (11.1)	6 (2.5)	0.051
Unsuspected PE	15 (55.6)	128 (53.3)	0.826
PESI	104 [91–118]	108 [100–117]	0.241
PESI class IV–V	13 (48.1)	138 (57.5)	0.353
DVT	9/12 (75.0)	46/66 (69.7)	0.439
Anticoagulation	24 (88.9)	196 (81.7)	0.435
Systemic thrombolysis	2 (7.4)	3 (1.3)	0.081
Vena cava filter placement	3 (11.1)	1 (0.4)	0.003
VTE recurrence	2 (7.4)	10 (4.2)	0.347
Adverse outcome	2 (7.4)	6 (2.5)	0.189
In-hospital mortality	1 (3.7)	19 (7.9)	0.704
PE-related mortality	0 (0.0)	2 (0.8)	>0.999

Table 3 (*continued*)

Table 3 (*continued*)

Parameters	Concurrent (n=27)	Sequential (n=240)	P
Histology of lung cancer			0.150
Adenocarcinoma	18 (66.7)	122 (50.8)	0.118
Squamous cell carcinoma	5 (18.5)	48 (20.0)	0.855
Small cell carcinoma	1 (3.7)	49 (20.4)	0.036
Large cell carcinoma	1 (3.7)	5 (2.1)	0.476
Other non-small cell carcinoma[#]	2 (7.4)	16 (6.7)	0.701
Initial stage of lung cancer			0.004
I	6 (22.2)	18 (7.5)	0.011
II	1 (3.7)	15 (6.3)	>0.999
III	1 (3.7)	66 (27.5)	0.004
IV	19 (70.4)	141 (58.8)	0.243
Lung cancer stage at the diagnosis of PE			<0.001
I	6 (22.2)	8 (3.3)	<0.001
II	1 (3.7)	10 (4.2)	>0.999
III	1 (3.7)	58 (24.2)	0.013
IV	19 (70.4)	164 (68.3)	0.829
Survival after the diagnosis of lung cancer (days)	214 [19–409]	498 [430–566]	<0.001
Survival after the diagnosis of PE (days)	185 [30–340]	224 [174–274]	0.889

Data are presented as mean ± SD, median [IQR] or n (%). *, chronic lung disease includes chronic obstructive pulmonary disease, asthma, bronchiectasis, idiopathic pulmonary fibrosis, pneumoconiosis, and tuberculosis-destroyed lung; [#], other non-small cell carcinoma includes non-small cell carcinoma (n=15), adenosquamous cell carcinoma (n=1), sarcomatoid carcinoma (n=1), and adenocarcinoma combined with large cell carcinoma (n=1). PE, pulmonary embolism; VTE, venous thromboembolism; TB, tuberculosis; NTM, nontuberculous mycobacteria; PESI, pulmonary embolism severity index; DVT, deep vein thrombosis; SD, standard deviation; IQR, interquartile range.

Table 4 Comparisons of laboratory and computed tomographic findings between concurrent and sequential groups

Parameters	Concurrent (n=27)	Sequential (n=240)	P
Laboratory findings			
NT-proBNP (pg/mL)	298 [95–799][&]	207 [79–505][†]	0.757
Troponin I (ng/mL)	0.022 (0.010–0.040)[&]	0.040 (0.015–0.060)[§]	0.542
CT findings			
Central PE*	5 (18.5)	43 (17.9)	0.938
RV dilation[#]	14 (51.9)	41 (17.1)	<0.001
Pulmonary infarction	3 (11.1)	15 (6.3)	0.406
Pleural effusion	4 (14.8)	35 (14.6)	>0.999

Data are presented as median [IQR] or n (%). *, central pulmonary arteries mean the right or left pulmonary artery or a more proximal location; [#], RV dilation was defined as RV to LV diameter ratio ≥1; [&], n=19; [†], n=124; [§], n=131. NT-proBNP, N-terminal-pro-B-type natriuretic peptide; CT, computed tomography; PE, pulmonary embolism; IQR, interquartile range; RV, right ventricular; LV, left ventricular.

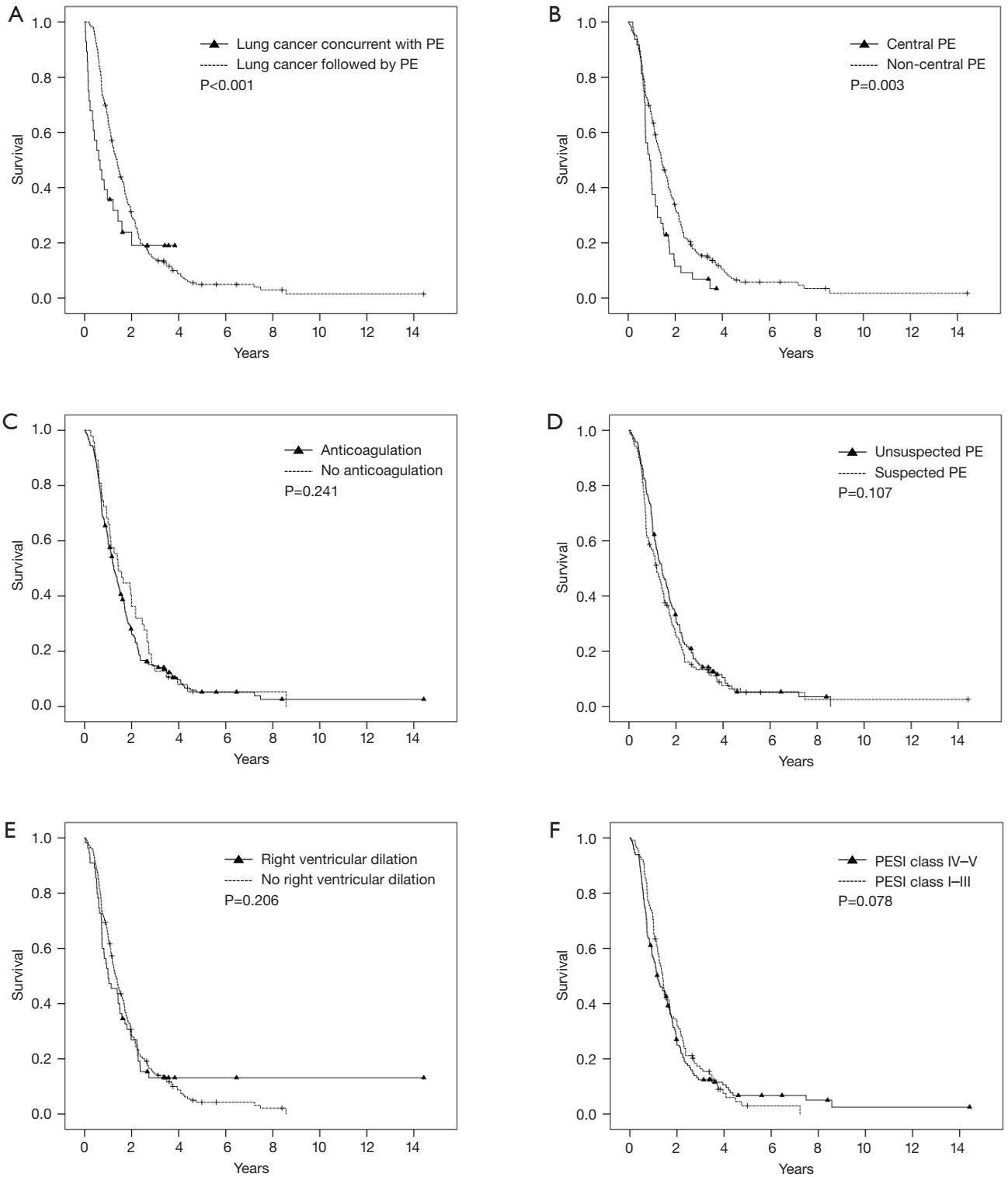

Figure 1 Kaplan-Meier plots of survival since the diagnosis of lung cancer by PE-related factors, including timing of PE presentation (A), central PE (B), anticoagulation (C), unsuspected PE (D), RV dilation (E), and PESI IV–V (F). P values were obtained using Cox proportional hazards model after adjusting for age, sex, smoking status, histologic type, and stage. PE, pulmonary embolism; PESI, pulmonary embolism severity index.

procoagulant secretion (24) and activate platelets and induce formation of microthrombi in the microvasculature (25). A previous study demonstrated that patients with adenocarcinoma of the lung had a higher risk of VTE than patients with squamous cell carcinoma, after adjusting for therapy and distant metastasis (25). Likewise, in the present study, the most common histology was adenocarcinoma, followed by squamous cell carcinoma and small cell carcinoma. Interestingly, in small cell lung cancer, almost all emboli, except for one, developed sequentially after the diagnosis of lung cancer, suggesting that PE is more likely to be provoked by chemotherapy rather than lung cancer itself. A recent study showed that cisplatin-based chemotherapy might be a strong predictor for the risk of thromboembolic events in small cell lung cancer (26). The most common risk factor for PE in patients with lung cancer was chemotherapy, in accordance with previous reports that chemotherapy increases the risk of VTE in patients with cancer (1-6), with a three-fold increased risk in lung cancer (25). The mechanism underlying the manner in which chemotherapy contributes to VTE risk has not been established. However, release of procoagulants and cytokines from cancer cells, direct endothelial damage, and down regulation of endogenous anticoagulants are likely to be involved in the pathogenesis of VTE in patients with cancer (27).

Patients with lung cancer and concurrent PE constituted approximately 10% of all patients with lung cancer and PE in the present study. The concurrent group had higher percentages of risk factors for VTE not directly related to lung cancer (immobilization, surgery or trauma, previous VTE). Thus, the possibility that provoking risk factors for VTE might contribute to the development of PE cannot be excluded. As reported in previous studies (6,11), most patients with PE had advanced stage lung cancer in the present study. However, early stage (stage I) lung cancer was significantly more common and stage III was significantly less common in the concurrent group. Furthermore, although anti-cancer therapy such as chemotherapy is an important risk factor for VTE in patients with lung cancer, it did not influence the occurrence of PE in the concurrent group. These findings suggest that prothrombotic activity of tumor cells plays a more important role in the occurrence of PE in the concurrent group. Compared with the sequential group, systemic thrombolysis and vena cava filter placement were more commonly used in the concurrent group: all patients had stage IV lung cancer. In addition, the concurrent group exhibited higher rates of RV dilation. These results imply that the concurrent group was associated with a more severe PE. In contrast, the frequency of central PE in the concurrent group did not differ from that in the sequential group. This can be partly explained by the finding that multiple lobar artery involvement by PE was significantly more common in the concurrent group than in the sequential group [10/12 (83.3%) *vs.* 17/79 (21.5%), P<0.001].

Concurrence of lung cancer with PE and central PE were significant prognostic factors for patients with lung cancer and PE. In the present study, in comparison with PE sequential to lung cancer, lung cancer concurrent with PE demonstrated reduced survival. Cancer patients who develop VTE have a higher mortality compared to those without VTE and with the same stage (23), suggesting that VTE is a marker for a more biologically aggressive tumor (12). From this point of view, we speculate that lung cancer concurrent with PE had more biologically aggressive tumor behavior than lung cancer with sequential PE (12). Although both RV dilation and central emboli were significant markers for a short-term prognosis in PE (14), central PE, not RV dilation, was an independent predictor of mortality in patients with lung cancer and PE. This finding can be explained by the notion that the size of emboli or the clot burden is more likely to contribute to the prognosis in these patients, rather than RV dysfunction. A previous study showed that anticoagulation therapy for unsuspected PE was associated with increased overall survival in patients with lung cancer (13). In contrast, whether patients with lung cancer and PE underwent anticoagulation or not did not affect the survival of these patients in the present study. This discrepancy can be partially explained by the finding that patients who did not receive anticoagulation had significantly higher proportion of peripheral PE (segmental or subsegmental) than patients who underwent anticoagulation [35/47 (74.5%) *vs.* 92/220 (41.8%), P<0.001].

Several limitations of the present study should be mentioned. First, selection bias was unavoidable due to the retrospective nature of the study. Although we searched the database of patients with PE, electronic medical records under the diagnosis codes, and CT readings, the possibility that some patients were omitted from selection could not be excluded. Second, missing laboratory data, such as NT-proBNP levels, could have influenced our results. Third, the fact that PE-specific therapy, such as anticoagulation, determined on clinician judgment may have affected the clinical outcome. Lastly, the causes of deaths were not

identified in approximately half of the patients.

Conclusions

Lung cancer with concurrent PE, found in approximately 10% of all patients with lung cancer and PE, was associated with more severe PE and infrequent small cell carcinoma. The timing of PE presentation (concurrence of lung cancer and PE) and the size of emboli (central PE) were independent predictors of death in patients with lung cancer patients and PE.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Review Board of each hospital (KNUH IRB 2016-09-020 and KNUMC 2016-10-005), which waived the requirement for written informed consent because of the retrospective nature of the study.

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