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Characteristics and 6-Month Mortality of Medical Oncology Patients With Incidental and Symptomatic Pulmonary Embolism: A Single-Institutional Retrospective Longitudinal Analysis

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Abstract

This study aimed to identify clinical characteristics of cancer patients with incidental pulmonary embolism (IPE) and assess the variables associated with 30-day mortality in cancer patients with PE including symptomatic pulmonary embolism (SPE) and IPE. 6-Month mortality rate in cancer patients with SPE and IPE were also compared. We retrospectively analyzed electronic medical records of cancer patients with newly diagnosed PE between January 2016 and June 2021. We compared clinical and radiological characteristics in cancer patients with IPE and SPE and identified variables associated with the overall 30-day mortality on multivariate analysis. All patients were followed up for 6 months and survival analysis was performed by use of Kaplan–Meier. Five hundred and nine eligible cancer patients with pulmonary embolism were identified during the study period. IPE is associated with lower BMI, colorectal and pancreas cancers, stage III/IV of cancer, recent antiangiogenic therapy, central venous catheter (CVC) and chronic cardiac or respiratory disease compared to SPE. The factors associated with 30-day mortality included poor performance status, lung/pleura or upper gastrointestinal cancers, stage III/IV of cancer, previous VTE, oxygen saturation < 95%, lactic acid > 2 mmol/l and bilateral PE. The overall survival in patients with IPE at 6-month follow-up was similar to those diagnosed with SPE. The present study has allowed the identification of factors associated with 30-day mortality in cancer patients with IPE and SPE. We also found similar mortality rate in cancer patients with IPE compared with patients with SPE at 6-month follow-up.

Keywords

pulmonary embolism, cancer, survival time, prognosis, anticoagulation

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Introduction

It is well-established that cancer is one of the major acquired risk factors for venous thromboembolism (VTE) with a fourfold to sevenfold increased risk to develop the disease.[1] Data from multiple studies suggest up to 20% of cancer patients develop VTE, including pulmonary embolism (PE) which is the second leading cause of death after the cancer itself in this group.[1,2] In turn, cancer has been found to be an independent predictor of death in series of patients with acute PE[3] and has been included as a predictive variable in validated PE prognostic models.[4,5]

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Traditionally, the examination of a patient for PE has included nuclear medicine ventilation-perfusion scanning and conventional pulmonary angiography. Computed tomographic (CT) pulmonary angiography enables less invasive, direct demonstration of clots within the pulmonary artery system and has become the standard imaging method for the evaluation of PE in many institutions. The technical advances that have made CT pulmonary angiography possible have been extended to routine thoracic CT. These advances include thinner collimation, breath-hold acquisitions, and optimized intravenous administration of contrast media. Although the technique used to perform routine thoracic CT differs from that used to perform CT pulmonary angiography, many routine thoracic CT examinations are adequate for the evaluation of PE. In addition to the growing utilization of thoracic CT, particularly in patients with malignancy, the detection of incidental pulmonary embolism (IPE) has become relatively common. IPE also known as clinically unsuspected or asymptomatic PE, refers to PEs detected on scans ordered for reasons other than suspicion of PE. In the oncological setting, these scans are usually performed for cancer staging, treatment evaluation or cancer recurrence detection.[6-8] Despite being unsuspected or asymptomatic, IPE in oncology patients is not necessarily a benign finding. Data from multiple studies suggest that the embolic burden in IPE is similar to that in symptomatic or suspected PE (SPE).[9-11] IPE could have an adverse impact on patient survival and previous studies have shown that most fatal PEs tend to be clinically unsuspected.[12] In addition, similar rates of recurrent VTE, major bleeding, and mortality have been observed on comparing patients with IPE to those with symptomatic PE.[11,13] Thus, in the absence of data from controlled trials, international clinical guidelines currently recommend that incidental VTE be treated similarly to symptomatic thrombosis.[14,15]

Nonetheless, only a few studies have evaluated the specific predictors of adverse outcomes in patients with cancer-associated pulmonary embolism, particularly in cases of IPE. Whether the clinical features for IPE differ from those of clinically SPE in patients with cancer is unclear. Whereas it has been clearly established that SPE in patients with cancer causes significant morbidity and mortality,[16] there is a lack of knowledge on the outcome of IPE in patients with cancer and few data to compare the survival time of cancer patients with IPE and SPE.

In the current retrospective study, we aim to identify important clinical characteristics and assess the variables associated with 30-day mortality in patients with solid organ malignancies with PE including SPE and IPE events in a single institution across a 5.5-year period. We also compared mortality rate in cancer patients with IPE with patients with SPE at 6-month follow-up.

Methods

Participants and Study Design

The study design was a single-center retrospective cohort study and was conducted at the Sir-Run-Run-Shaw Hospital affiliated to Zhejiang University School of Medicine, a large metropolitan teaching hospital in China. The hospital's ethics committee granted ethical approval of this study.

This research involved adult cancer patients who were diagnosed by histologic or cytological examination at Sir-Run-Run-Shaw Hospital and who had pulmonary embolus objectively confirmed by standard radiological methods between January 2016 and June 2021. Patients with the following characteristics were excluded from the study: age < 18 years, hematologic malignancy, CT scan quality did not allow PE assessment or radiological data of PE not available, cancer in remission (without disease or treatment for 1 year), incomplete patients data or incomplete follow-up or tumoral thrombi.

Data Collection

The institutional electronic medical record systems were used to extract the needed data. The following demographic and clinical data were comprehensively reviewed and collected by trained physicians, including age, gender, VTE history, chronic cardiopulmonary conditions, body weight, performance status according to the World Health Organization criteria, cancer type and stage, arterial blood gas analysis at the time of diagnosis of PE, anticancer therapies within 1 month before pulmonary embolism. Whether PE was clinically suspected or not was also recorded for each patient. The patients were divided into incidental and symptomatic cohorts based on a chart review of clinical history. The PE was considered as SPE if a dedicated CTPA study was ordered by the referring physician, and considered IPE if the PE was detected on routine staging or follow-up CT scans or for other reasons. The most proximal location of PE was recorded based on the radiology reports. The location of PE was categorized as main, lobar, segmental or subsegmental and one-sided or bilateral lung involvement. When PE involved multiple locations, the most proximal location was recorded. PE involving main or lobar pulmonary arteries was considered to be proximal, and that involving segmental and subsegmental arteries was considered to be distal. Questionable radiology reports were verified by two senior thoracic radiologists. The patients were also followed-up to ascertain the patients' outcome during 6 months following the initial diagnosis with PE. Follow-up data were retrieved from the electronic medical records of patients, including: (1) initial and subsequent anticoagulant treatment or thrombolytic therapy (recombinant tissue plasminogen activator [rt-PA], unfractionated heparin or low molecular weight heparin [LMWH], warfarin, direct oral anticoagulant) and the use of inferior vena cava (IVC) filters. Treatment in the first 30 days was defined as initial treatment, treatment beyond the first 30 days as subsequent treatment; (2) Evolution of the underlying cancer; (3) Death, evolution of the PE confirmed by spiral CT pulmonary arteriography and major bleeds defined according to ISTH guidelines.[17]

Statistical Analysis

Continuous variables were presented as median and interquartile rang (IQR, 25th-75th), and were compared using either a

t-test or Mann–Whitney *U* test, as appropriate. Categorical variables were presented as number and percentage (*n*, %), and were compared using the Chi-squared test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to identify the variables associated with 30-day mortality. First, univariate logistic regression analysis was used to screen the independent factors associated with 30-day mortality, and in order to avoid risk factor omission, the variables displaying a *P*-value < .2 in the univariate analysis were then included into the multivariate logistic regression analysis. Overall survival at 6 months of follow-up was estimated with the Kaplan–Meier method and comparisons between the symptomatic PE and incidental PE groups, the proximal PE and distal PE groups and bilateral PE and one-sided PE groups were made using the log-rank test. All statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Two-sided $P < .05$ was considered to be significant.

Results

Patient Characteristics

A total of 509 eligible cancer patients with pulmonary embolism were finally enrolled in the study, including 264 with SPE and 245 with IPE (Figure 1). Twenty-nine (5.3%) and 12 (2.2%) cancer patients with PE were excluded due to missing important values and incomplete follow-up, respectively (Figure 1). The majority ($n = 203$; 76.9%) of the IPE was detected on CT scans performed for the diagnoses, staging, or treatment evaluation of the malignancy. The other 61 were diagnosed during CT examinations performed for the evaluation of other acute medical illnesses, including abscess detection in postoperative patients. Table 1 summarizes the baseline characteristics of patients with IPE and SPE. BMI was significantly lower in the IPE group than SPE group (23.1 vs 25.1, $P < .001$). We found that those with IPE were more likely to have colorectal and pancreas cancers, stage III/IV of cancer, antiangiogenic therapy, central venous catheter (CVC), chronic cardiac or respiratory disease compared to patients with SPE. Conversely, central nervous system, lung/pleura and endocrine cancers, immunotherapy were more frequently observed in patients with SPE. Table 2 summarizes the location of IPE and SPE. While SPE was more likely to be proximal, involving main and/or lobar pulmonary arteries than IPE, this did not meet the criteria for statistical significance (98/245, 40.0% in SPE group vs 87/264, 33.0% in IPE group, respectively) (Figure 2, Table 2). Notably, patients with SPE more frequently involved bilateral lung than patients with IPE (210/245, 87.5% in SPE group vs 143/264, 54.2% in IPE group, $P < .001$) (Figure 2, Table 2).

Factors Associated with 30-Day Mortality

Sixty-six patients died during the first 30 days after diagnosis of PE, including 27 patients (10.2%) with IPE and 39 patients (15.9%) with SPE. The univariate analysis showed that age ($P = .011$), performance status > 1 ($P < .001$), lung/pleura cancer ($P = .005$), upper gastrointestinal cancers ($P = .024$), stage III/IV of cancer($P < .001$), radiotherapy history ($P = .035$), CVC ($P = .043$), previous VTE ($P = .016$), SPE (vs overall IPE) ($P = .028$), oxygen saturation < 95% ($P < .001$), lactic acid > 2 mmol/l ($P = .022$), proximal PE ($P = .005$), and bilateral PE ($P = .012$) were associated with 30-day mortality, the difference were statistically significant (Table 3).

The multivariate analysis showed that performance status >1 ($P < .001$), lung/pleura cancer ($P = .041$), upper gastrointestinal cancers ($P = .002$), stage III/IV of cancer ($P < .001$), previous VTE ($P = .008$), oxygen saturation < 95% ($P = .001$), lactic acid > 2 mmol/l ($P = .0147$), and bilateral PE ($P = .031$) were independently associated with death at the 30-day follow-up. The analysis was stratified for the gravity assessment of PE for 30-day survival. Notably, neither chronic cardiac or respiratory diseases nor proximal PE (vs distal PE) was associated with 30-day mortality in our study (Table 3).

6-Month Follow-Up

The overall mortality rates at the 6-month follow-up were 19.1% considering the whole cohort. The mortality rates were higher in patients with SPE than in those with IPE at 6 months, but the difference did not reach statistical significance (47/264, 17.8% in IPE group vs 57/245, 23.3% in SPE group, respectively). Figure 3a shows the overall survival curves at the 6-month follow-up between IPE and SPE groups, which did not demonstrate significant difference(log-rank $P = .214$). Similarly, the difference did not reach statistical significance on comparing patients with proximal PE to distal PE at 6-month overall survival (log-rank $P = .385$) (Figure 3b). Notably, patients with one-sided PE had a higher 6-month overall survival than those with bilateral PE after adjustment for the gravity assessment of PE (log-rank $P = .006$) (Figure 3c).

Anticoagulation Therapy and Outcomes

Details on the type of anticoagulation therapy were provided in Table 4. In initial treatment, most of the cases (64.6%) were treated with LMWH, with no difference between the IPE and SPE groups (168/264, 63.6% vs 161/245, 65.7%, respectively). In IPE group, 7 patients with IPE were asymptomatic at the time of diagnosis of pulmonary embolism, but the disease progressed rapidly requiring thrombolytic therapy within the next few days. rt-PA thrombolysis was totally prescribed to 2.7% of patients in the incidental group and 9.4% of the patients of symptomatic group, and the difference was statistically significant ($P = .001$). There were no significant differences in unfractionated heparin, direct oral anticoagulants (DOACs) or IVC filter placement between the two groups as initial treatment.

In subsequent therapy, DOACs were prescribed to 65.9% of patients in IPE group and 54.7% of the patients of SPE group ($P < .001$). These new agents may offer a significant

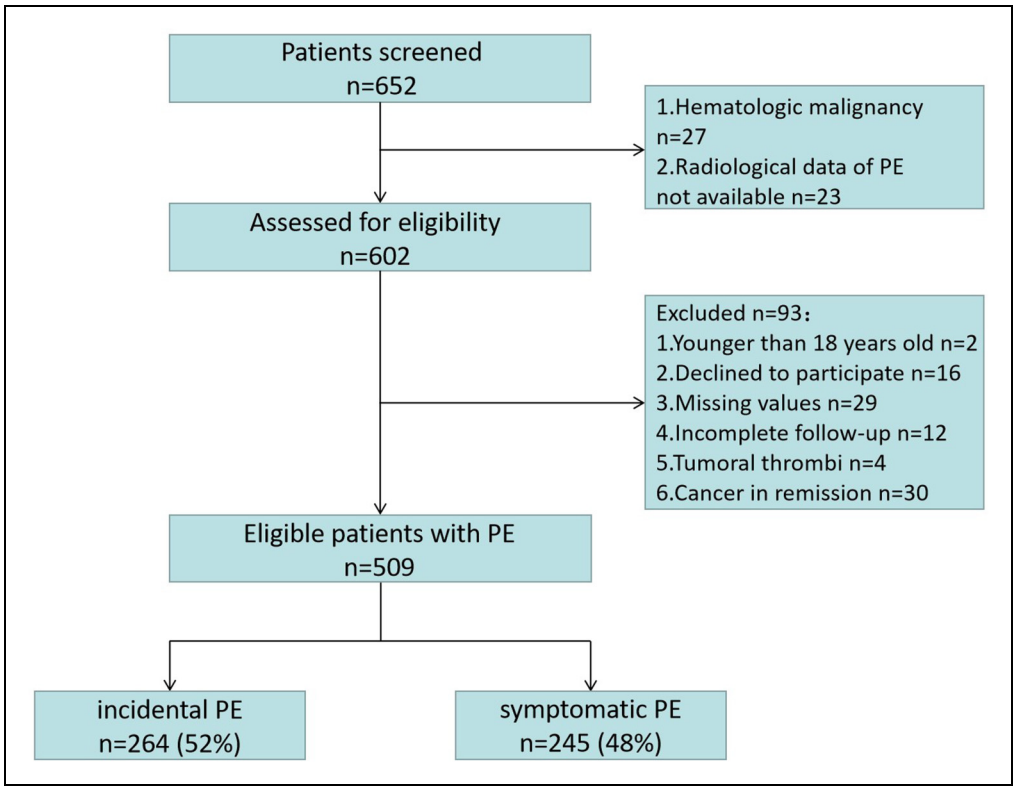

Figure 1. Study flowchart diagram. PE: pulmonary embolism; CT: computed tomography.

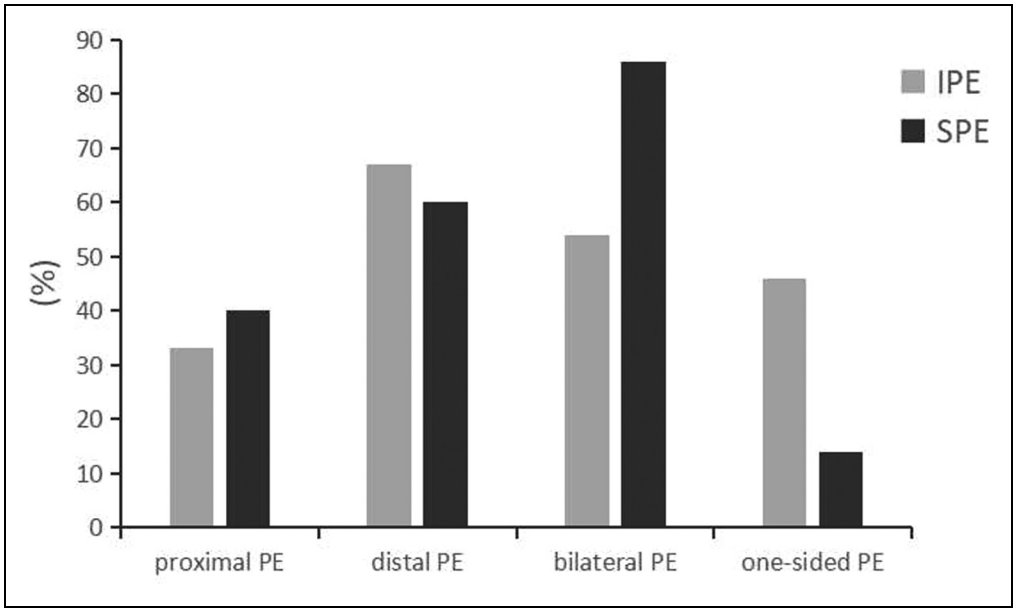

Figure 2. Comparison of location of IPE and SPE. IPE, incidental pulmonary embolism; SPE, symptomatic pulmonary embolism.

improvement in quality of life for these patients that were exposed to a long-term treatment. All 77 patients received no subsequent treatment, including 34 patients in IPE group and 43 patients in SPE group and the difference was not statistically significant (12.9% in IPE group vs 17.6% in SPE group, respectively). The reasons for no subsequent treatment other than death were active bleeding in 7 patients, thrombocytopenia in 6 patients, and brain metastasis in 4 patients. IVC filter was placed in 6 patients who were previously on anticoagulation, 3 patients in each group. Clinically relevant bleeding events occurred in 10.4% of patients who treated with anticoagulant (3.3% major bleeding and 7.1% minor bleeding, respectively).

Table 1. Baseline Characteristics of the IPE and SPE Group at the Time of Inclusion.

	IPE	SPE	*P*
Total *n*	264	245	
Female, *n*(%)	119 (45.1)	119 (48.6)	NS
Age (years)	63.9 (56.0-71.5)	63.8 (58.1-71.4)	NS
BMI	23.1 (20.9-25.8)	25.1 (22.1-27.9)	<.001
PS, *n*(%)			
0-1	213 (80.2)	209 (85.3)	NS
2-4	51 (19.2)	36 (14.7)	
Tumor type, *n*(%)			
CNS	7 (2.7)	38 (15.5)	<.001
Colorectal	58 (22.0)	23 (9.4)	<.001
Pancreas	21 (8.0)	7 (2.9)	.012
Lung/pleura	54 (20.5)	73 (29.8)	.015
Upper GI	31 (11.7)	23 (9.4)	NS
Hepatobiliary	26 (9.8)	15 (6.1)	NS
KUB	14 (5.3)	9 (3.7)	NS
FGT	21 (8.0)	13 (5.3)	NS
Musculoskeletal	6 (2.3)	8 (3.3)	NS
Melanoma/skin	4 (1.5)	6 (2.4)	NS
MGT	1 (0.4)	4 (1.6)	NS
HNF	3 (1.1)	7 (2.9)	NS
Breast	18 (6.8)	13 (5.3)	NS
Endocrine	0 (0.0)	6 (2.4)	.012
Adenocarcinoma, *n*(%)	180 (68.2)	149 (60.8)	NS
Cancer stage, *n*(%)			
I/II	66 (25.0)	86 (35.1)	.013
III/IV	198 (75.0)	159 (64.9)	
Anticancer therapy 30 days prior to PE, *n*(%)			
Surgery	55 (20.8)	44 (18.0)	NS
Radiotherapy	13 (4.9)	19 (7.8)	NS
Chemotherapy	104 (39.4)	77 (31.4)	NS
Antiangiogenic therapy	19 (7.2)	6 (2.4)	.013
Targeting therapy	23 (9.8)	26 (10.6)	NS
Immunotherapy	14 (5.3)	26 (10.6)	.041
Hormone therapy	8 (3.0)	7 (2.9)	NS
CVC, *n*(%)	192 (72.7)	132 (53.9)	<.001
Previous VTE, *n*(%)	41 (15.5)	29 (11.8)	NS
Chronic cardiac or respiratory disease, *n*(%)	97 (39.4)	67 (27.3)	.023

Abbreviations: IPE, incidental pulmonary embolism; SPE, symptomatic pulmonary embolism; CVC, central venous catheter; BMI, body mass index; PS, performance status; VTE, venous thromboembolism; CNS, central nervous system; upper GI, upper gastrointestinal; FGT, female genital tract; KUB; kidney, ureter and bladder; MGT, male genital tract; HNF, head, neck and face; NS, not significant.

Table 2. Comparison of Location of IPE and SPE.

	IPE($n = 264$)	SPE($n = 245$)	*P*
Proximal PE, *n*(%)	87 (33.0)	98 (40.0)	NS
Distal PE, *n*(%)	177 (67.0)	147 (60.0)	
Bilateral PE, *n*(%)	143 (54.2)	210 (85.7)	<.001
One-sided PE, *n*(%)	121 (45.8)	35 (14.3)	

Abbreviations: IPE, incidental pulmonary embolism; SPE, symptomatic pulmonary embolism; NS, not significant.

Forty-seven deaths (17.8%) in IPE group and 57 deaths (22.9%) in SPE group were reported after 6-month follow-up while the other cases showed improvement or got cured (79.6%) in the 6-month follow-up.

Discussion

This study aimed to compare the clinical features of oncology patients with symptomatic or incidental PE and assess the variables associated with 30-day mortality and clinical outcomes after initial and subsequent therapy for PE. We found that the IPE is associated with lower BMI, colorectal and pancreas cancers, stage III/IV of cancer, recent antiangiogenic therapy, CVC, and chronic cardiac or respiratory disease. The factors associated with 30-day mortality included poor performance status, lung/pleura or upper gastrointestinal cancers, stage III/IV of cancer, previous VTE, oxygen saturation < 95%, lactic acid > 2 mmol/l, and bilateral PE and the overall survival in patients with IPE at 6-month follow-up was similar to those diagnosed with symptomatic PE.

Among the potential factors associated with 30-day mortality identified, we would like to point out that poor performance status and advanced cancer stage were particularly robust and consistent with previous studies on SPE in the general population and in patients with cancer.[18,19] In a recent study, Farmakis et al[20] investigated the impact of performance status, both at diagnosis and at the follow-up visits, on long-term outcomes related to VTE and reported a significant association between poor performance status and long-term VTE related clinical outcomes such as VTE recurrence and major bleeding, in patients with cancer-associated PE. In particular, changes in performance status during follow-up were a stronger predictor of VTE recurrence or major bleeding than performance status at baseline, indicating that serial monitoring of performance status over follow-up may have held additional prognostic information. However, our study was unable to reach the same conclusion because performance status was not followed up. This study demonstrated that a history of VTE was associated with increased mortality. Moreover, our study identified some novel variables which may be potentially useful for predicting the overall 30-day mortality, including: lung/pleura cancers, upper GI cancers, and bilateral PE. Previous study demonstrated that lactic acid has been linked to a greater risk of short-term mortality in patients with PE with a low-intermediate risk, independent of other gas-analytic parameters.[21] However, cancer patients were excluded from that study. The present study is the first, to our knowledge, to mention elevated lactic acid levels as a possible indicator of asymptomatic PE among cancer patients. Notably, age, chronic cardiac or respiratory disease were not associated with short-term mortality in our study in contrast to previous pulmonary embolism prognostic models for acute SPE in the general population[4,5] and in cancer patients.[18,19] When multivariable analysis was performed with all variables that were significantly associated with mortality in the univariate analysis, IPE was not significantly associated with mortality. Thus, our

Table 3. Univariate and Multivariate Analysis of Covariates Associated with the Overall 30-Day Mortality in the Whole Cohort.

			Univariate Analysis		Multivariate Analysis	
	Alive at 30 Days	Dead at 30 Days	OR (95% CI)	*P*	OR (95% CI)	*P*
Total *n*	443 (87.0)	66 (13.0)				
Female, *n*(%)	212 (49.9)	26 (39.4)		NS		
Age (years)	61.4 (48.2-68.9)	65.3 (51.5-71.8)	1.02 (1.00-1.03)	.011		NS
BMI	24.6 (21.3-26.8)	25.1 (22.6-28.1)		NS		
PS, *n* (%)						
0-1	399 (85.6)	31 (47.0)	5.78 (4.27-9.00)	<.001	2.98 (1.67-5.48)	<.001
2-4	52 (14.4)	35 (53.0)				
Tumor type, *n* (%)						
CNS	38 (8.6)	7 (10.6)		NS		
Colorectal	77 (17.4)	4 (6.1)	0.55 (0.25-0.89)	.016		NS
Pancreas	24 (5.4)	4 (6.1)		NS		
Lung/pleura	103 (23.3)	24 (36.4)	2.33 (1.45-3.83)	.005	1.23 (1.03-3.38)	.041
Upper GI	43 (9.7)	11 (16.7)	2.08 (1.35-3.22)	.024	2.25 (1.68-4.45)	.002
Hepatobiliary	38 (8.6)	3 (4.5)		NS		
KUB	21 (4.7)	2 (3.0)		NS		
FGT	28 (6.3)	6 (9.1)		NS		
Musculoskeletal	13 (2.9)	1 (1.5)		NS		
Melanoma/skin	10 (2.3)	0 (0.0)		NS		
MGT	5 (1.1)	0 (0.0)		NS		
HNF	9 (2.0)	1 (1.5)		NS		
Breast	28 (6.3)	3 (4.5)		NS		
Endocrine	6 (1.4)	0 (0.0)		NS		
Adenocarcinoma, *n* (%)	168 (38.0)	21 (31.8)		NS		
Cancer stage, *n* (%)						
I/II	305 (68.8)	22 (33.3)	4.46 (2.63-7.81)	<.001	2.25 (1.43-4.42)	<.001
III/IV	138 (31.2)	44 (66.7)				
Anticancer therapy 30 days prior to PE, *n* (%)						
Surgery	83 (18.7)	16 (24.2)		NS		
Radiotherapy	24 (5.4)	8 (12.1)	1.72 (1.03-2.52)	.035		NS
Chemotherapy	159 (35.9)	22 (33.3)		NS		
Antiangiogenic therapy	22 (5.0)	3 (4.5)		NS		
Targeting therapy	44 (9.9)	5 (7.6)		NS		
Immunotherapy	32 (7.2)	8 (12.1)		NS		
Hormone therapy	11 (2.5)	4 (6.1)		NS		
CVC, *n* (%)	273 (61.6)	51 (77.3)	1.64 (1.22-2.74)	.043		NS
Previous VTE, *n* (%)	54 (12.2)	16 (24.2)	1.78 (1.27-2.59)	.016	2.05 (1.36-4.38)	.008
Chronic cardiac or respiratory disease, *n* (%)	141 (31.8)	23 (34.8)		NS		
IPE, *n* (%)	237 (53.5)	27 (40.9)	1.56 (1.26-2.43)	.028		NS
SPE, *n* (%)	206 (46.5)	39 (59.1)				
Arterial blood gas analysis, *n* (%)						
Oxygen saturation (normal range, 95%-100%) < 95%	192 (43.3)	44 (66.7)	3.89 (2.36-6.75)	<.001	2.43 (1.46-3.70)	.001
PO_2 (normal range, 75-100 mm Hg) < 75 mm Hg	201 (46.6)	36 (54.5)		NS		
Lactic acid (normal range, 0.5-2 mmol/l) > 2 mmol/l	148 (33.4)	34 (51.5)	1.76 (1.36-3.47)	.022	1.89 (1.52-3.79)	.014
Radiological findings, *n* (%)						
Proximal PE (vs distal PE)	147 (33.2)	38 (57.6)	1.84 (1.45-3.73)	.005		NS
Bilateral PE (vs one-sided PE)	301 (67.9)	52 (78.9)	2.33 (1.55-4.80)	.012	1.72 (1.03-2.52)	.031

Abbreviations: IPE, incidental pulmonary embolism; SPE, symptomatic pulmonary embolism; CVC, central venous catheter; BMI, body mass index; PS, performance status; VTE, venous thromboembolism; CNS, central nervous system; upper GI, upper gastrointestinal; FGT, female genital tract; KUB; kidney, ureter and bladder; MGT, male genital tract; HNF, head, neck and face; NS, not significant.

results may suggest that the higher mortality in cancer patients with PE is mainly related to the advanced cancer stage and the poor performance status of these patients rather than IPE.

In the study cohort, up to 51.9% of the diagnosed PEs were incidental, which is consistent with prior clinical and autopsy studies.[12,22] Those with IPE were more likely to have colorectal and pancreas cancers, receive antiangiogenic therapy and much higher with advanced stage than with early stage disease compared to those with SPE. Similar to the findings of the present study, Silva et al[23] found that PE was an incidental finding in

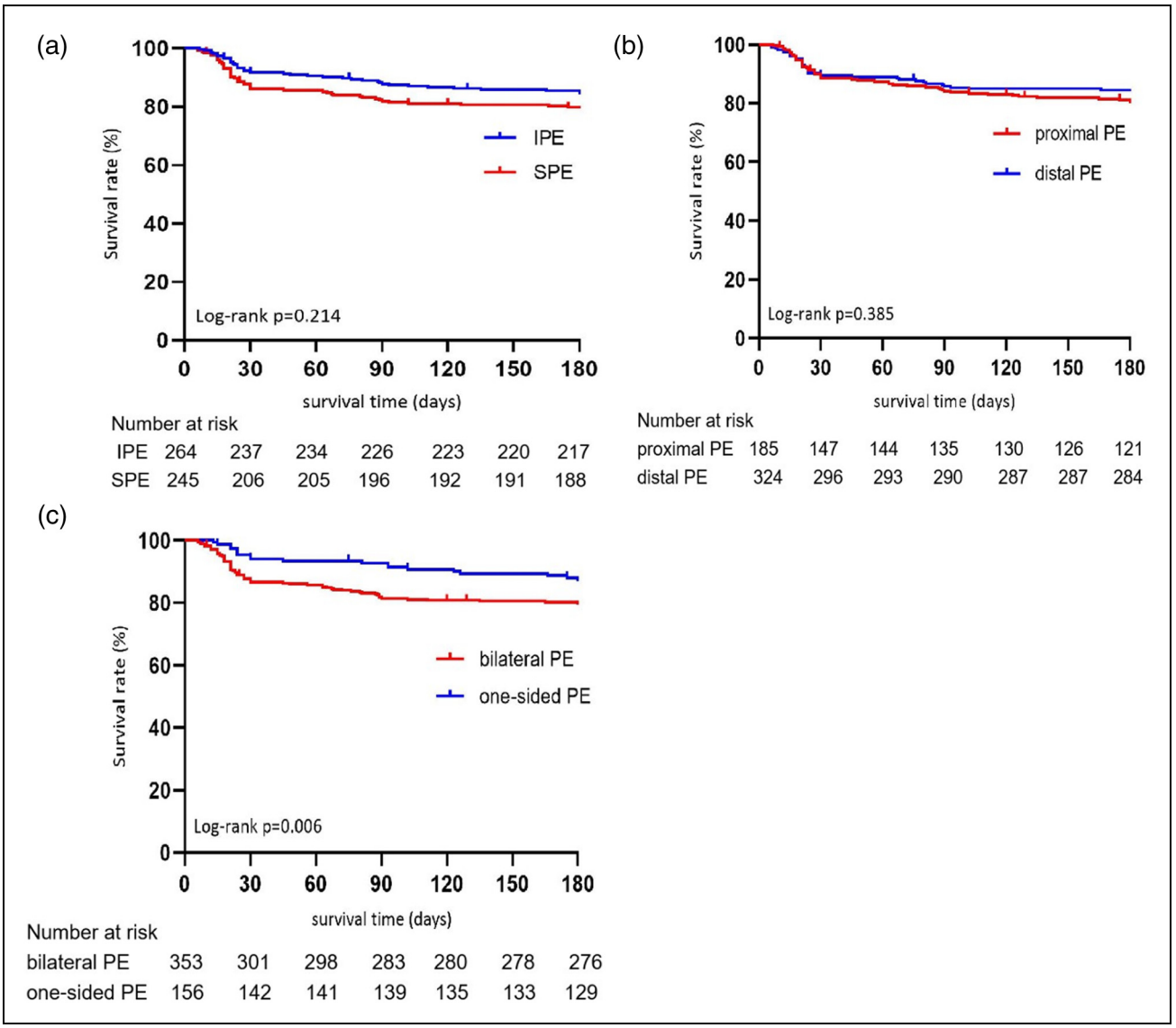

Figure 3. Kaplan–Meier curves. In detail: (a) Overall survival Kaplan–Meier curves at the 6-month follow-up according to IPE group and SPE group. SPE: symptomatic pulmonary embolism, IPE: incidental pulmonary embolism; (b) Overall survival Kaplan–Meier curves at the 6-month follow-up according to proximal PE group and distal PE group. PE: pulmonary embolism; (c) Overall survival Kaplan–Meier curves at the 6-month follow-up according to bilateral PE group and one-sided PE group. PE: pulmonary embolism.

69.4% of the oncologic patients and the most common type of cancer which developed IPE were colorectal and most of which had metastases. In the study by Abdel-Razeq et al,[24] it was demonstrated that the most frequent type of cancer in cancer patients with incidental PE were gastric and colorectal. Furthermore, most of the patients (77%) had already developed metastases at the time of IPE diagnosis. In addition, Chang et al[25] reported that among 703 cancer patients diagnosed with PE, IPE was identified in 474 (67.3%) patients. Compared to symptomatic patients, those with IPE had more advanced malignancy and were more likely to be on current antiangiogenic therapy at the time of IPE diagnosis. These findings indicate that clinicians need to be aware of this frequent complication in cancer patients with these clinical features, even in the absence of clinical symptoms. In our study, there was a seemingly higher incidence of symptomatic or incidental PE in certain cancer types. This difference did not meet statistical significance in most cancer groups, possibly due to the relatively small number of patients in each category. Further prospective studies with larger cohort are needed to better assess the results. The radiological characteristics of the PEs identified in this study demonstrated that most were distal PE, including segmental and subsegmental, and these characteristics were similar between symptomatic and incidental PEs, which is similar to what has been shown in previous studies.[26,27] It is interesting as one would expect incidental PEs to be more likely to be more peripheral and subsegmental compared with symptomatic PEs, but this was not the observation in our study. It is possible that patients with IPEs more commonly had cancers that are more thrombogenic than SPEs. However, the present study found that the proportion

Table 4. Treatment of Cancer Patients with SPE and IPE.

Treatment	IPE ($n = 264$)	SPE ($n = 245$)	*P*
Initial treatment (first 30 days), *n*(%)			
LMWH	168 (63.6)	161 (65.7)	NS
Unfractionated heparin	6 (2.3)	3 (0.8)	NS
Direct oral anticoagulants	59 (22.3)	48 (19.6)	NS
IVC filter placement	24 (9.1)	10 (4.1)	NS
Thrombolysis	7 (2.7)	23 (9.4)	.001
Subsequent treatment (after 30 days), *n*(%)			
LMWH	11 (4.2)	9 (3.7)	NS
Direct oral anticoagulants	174 (65.9)	134 (54.7)	.01
Warfarin	42 (15.9)	56 (22.9)	NS
IVC filter placement	3 (1.1)	3 (1.2)	NS
No subsequent therapy	34 (12.9)	43 (17.6)	NS

Abbreviations: IPE, incidental pulmonary embolism; SPE, symptomatic pulmonary embolism; LMWH, low molecular weight heparin; IVC, Inferior vena cava; NS, not significant.

of bilateral PE was significantly lower in the IPE group than in the SPE group. To the best of our knowledge, this has not been previously reported or investigated.

In the present study, we found that the 6-month mortality rates of IPE and SPE patients were well comparable. These findings are consistent with Dentali et al,[28] who found similar 6-month mortality rates for patients with cancer with asymptomatic and symptomatic VTE (51% and 48.6%, respectively), which were both significantly higher compared to the mortality rate of patients with cancer without VTE (27.1%). Similarly, the study by den Exter et al[13] compared the mortality of oncologic patients with SPE and IPE. The authors reported that survival at 12 months was not significantly different between patients with SPE versus IPE, with a rate of mortality of 52.9 and 53.3% in incidental and symptomatic patients, respectively. In another more recent study with a large cohort, Font et al[29] showed that the difference of overall 90-day mortality rate did not reach statistical significance on comparing patients with UPE and SPE (26.5% and 33%, respectively). Overall, incidental or unsuspected PE in cancer patients represents a frequent finding on CT scans ordered for reasons other than suspected PE, and it is likely to increase in the near future, due to the continuous improvement in CT scan technologies. Even if IPE is generally milder in the short-term, it seems to share a similar impact on survival as compared to SPE.

In the current study, the majority (88.2%) of the IPE group received anticoagulant treatment initially, a similar treatment as SPE group. There was no difference of the proportion of untreated patients between IPE and SPE groups. The incidental or suspected nature of PE had no bearing on treatment-related decisions. Despite receiving anticoagulant treatment, patients with cancer with IPE displayed a high recurrence rate,[13] which was even comparable to those with SPE. In our view, these results provide indirect evidence for a comparable treatment effect in both groups. However, our study was not designed to definitively determine whether anticoagulation therapy is indicated for these patients. Of note, current guidelines suggest that IPE should receive similar initial and long-term anticoagulant treatment as for symptomatic PE. However, direct evidence regarding the treatment of IPE is scarce and treatment indications are largely derived from studies performed in cancer patients with symptomatic VTE. Although no clear guidelines currently exist for the treatment of IPE, our results indicate that the general consensus is to use the same treatment strategy for both sets of patients in clinic.[11,13,29] Primarily, on the basis of the results of the CLOT (randomized comparison of LMWH vs oral anticoagulant therapy for the prevention of recurrent VTE in patients with cancer) trial,[14,30,31] evidence-based guidelines recommend at least 6 months of LMWH treatment for patients with VTE and cancer, and that LMWH is preferable to warfarin-based treatment. However, previous reports showed that most patients receive less than 3 months of LMWH treatment and are notably more likely to discontinue treatment in the real world.[32,33] This has been attributed to the burden of self-injection and the high cost of LMWH. The latest data showed that DOACs could emerge as an alternative to warfarin and LMWH for the treatment of cancer-associated VTE.[34,35] In this present study, we found that most of the patients received DOACs for subsequent treatment, which is consistent with early studies.

To the best of our knowledge, the present study is one of a limited number of studies to assess clinical features of IPE and differentiate them from SPE in China. This is also the first study to identify novel predictors of 30-day mortality and report short-term prognosis of IPE patients in a mixed inpatient population of China accompanied by reliable follow-up and outcome data. However, there are several limitations to our study. First, its retrospective design may enhance information bias. However, the well-established medical electronic records at Sir-Run-Run-Shaw Hospital made it possible to accurately identify PEs that were found incidentally on a chest CT study and collect related clinical and management data. Second, we did not have data regarding causes of death and so we cannot determine whether mortality was associated with the diagnosis of PE or concomitant illnesses. In addition, it is based on data from a single center that do not allow the generalization of conclusions. Thus, larger prospective studies, conducted in multiple cancer hospitals, are needed for better evaluation of the results.

In conclusion, the present study has allowed the identification of factors associated with 30-day mortality in cancer patients with incidental and symptomatic PE. We also found similar mortality rate in patients with cancer diagnosed with and treated for incidental PE compared with patients with cancer with symptomatic PE at 6-month follow-up. Given the limitations of this study, these findings need to be confirmed by larger prospective and/or interventional studies.

Declaration of Conflicting Interests

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