Characteristics and outcomes of cancer patients who develop pulmonary embolism: A cross-sectional study

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Abstract. Pulmonary embolism (PE), along with deep vein thrombosis, are collectively known as venous thromboembolism (VTE). Predisposing factors for PE include post-operative conditions, pregnancy, cancer and an advanced age; of note, a number of genetic mutations have been found to be associated with an increased risk of PE. The association between cancer and VTE is well-established, and cancer patients present a higher risk of a thrombotic event compared to the general population. In addition, PE is a significant cause of morbidity and mortality among cancer patients. The aim of the present study was to illustrate the clinical characteristics, laboratory findings, radiology features and outcomes of cancer patients who developed PE, collected from an anticancer hospital. For this purpose, adult cancer patients diagnosed with PE by imaging with computed tomography pulmonary angiography were enrolled. The following data were recorded: Demographics, comorbidities, type of cancer, time interval between cancer diagnosis and PE occurrence, the type of therapy received and the presence of metastases, clinical signs and symptoms, predisposing factors for PE development, laboratory data, radiological findings, electrocardiography findings, and the type of therapy received for PE and outcomes in a follow-up period of 6 months. In total, 60 cancer patients were enrolled. The majority of the cancer patients were males. The most common type of cancer observed was lung cancer. The majority of cases of PE occurred within the first year from the time of cancer diagnosis, while the majority of patients had already developed metastases. In addition, the majority of cancer patients had received chemotherapy over the past month, while they were not receiving anticoagulants and had central obstruction. A large proportion of patients had asymptomatic PE. The in-hospital mortality rate was 13.3% and no relapse or mortality were observed during the follow-up period. The present study demonstrates that elevated levels of lactic acid and an increased platelet count, as well as low serum levels of carcinoembryonic antigen, albumin and D-dimer, may be potential biomarkers for asymptomatic PE among cancer patients.

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Introduction

Pulmonary embolism (PE), which is the obstruction of the pulmonary arteries, is a part of venous thromboembolism (VTE) along with deep vein thrombosis (DVT). Globally,

PE represents the third most frequent cause of cardiovascular-related mortality, following stroke and myocardial infarction (1). The incidence of PE is similar in the USA and Europe, and it is estimated to be ~300,000 to 600,000 cases annually (1). There are several well-recognized genetic mutations responsible for the increased risk of PE (2). Major acquired predisposing factors include post-operative conditions, pregnancy, cancer and an advanced age (3).

The strong association between cancer and VTE is known, and cancer patients present a 6-7-fold greater risk of undergoing a thrombotic event compared to the general population. PE is a notable cause of morbidity and mortality in this group (4). The real prevalence of PE in patients with malignancy is probably underestimated (5). Of note, approximately half of the cases of PE among cancer patients were incidentally diagnosed by imaging. Advances in radiological techniques may have contributed to this fact (5).

The majority of cancer patients present with the upregulation of the coagulation cascade, and increased platelet activation and aggregation. The coagulation activation state in these patients appears to have a multifactorial underlying mechanism. Tumor cells may express prothrombotic molecules and may produce enzymes such as cysteine proteases, which directly result in clotting by activating factor X and produce physiological tissue factor, which is related to the activation of the extrinsic pathway of blood coagulation. Additionally, tumor cells can indirectly contribute to clotting by secreting cytokines that act on endothelial cells and mononuclear cells, thus stimulating the production of prothrombotic molecules (6).

It has been reported that patients with active cancer who have undergone surgery, particularly in the abdomen or pelvis, are subject to a higher risk of developing PE, which is affected by age, the presence of obesity, duration of the surgical procedure, long recovery times, radiotherapy and systemic therapy. In addition, chemotherapy and hormone therapy can induce both venous and arterial thrombosis. Furthermore, factors influencing the incidence of PE in cancer patients include the type of cancer, as well as the stage, type and duration of chemotherapy, the response to therapy, nutritional status, an individual's mobility, and liver and kidney functional status (7).

In Greece, few studies have reported data associated with pulmonary embolism in cancer patients (8,9). The aim of the present study was to illustrate the clinical characteristics, laboratory findings, radiology features and outcomes of individuals with malignancy who developed PE, collected from an anticancer hospital in Greece. The present study was designed in order to identify possible additional predisposing factors for PE among cancer patients and potential biomarkers indicative of PE, particularly in asymptomatic cancer patients.

Patients and methods

Study design. The design of the present study was cross-sectional. The present study obtained approval from the Institutional Board of Agios Savvas Hospital (protocol no. 8034/1-12-18). The study was in line with the declaration of Helsinki in 1995 (revised in Edinburgh 2000). This research involved adult cancer patients who visited Agios Savvas Anticancer Hospital (Athens, Greece) and who were diagnosed with PE by imaging with computed tomography (CT) pulmonary angiography (CTPA). Another inclusion criterion was a Miller index point score ≥1, which indicates either the obstruction of a segmental artery or at least a moderate reduction in the peripheral perfusion of a lung zone (10). The exclusion criteria were evidence of previous PE, inconclusive findings due to poor imaging quality and multiple primary malignancy sites. The aim of the present study was to record the clinical, radiological and laboratory data of these patients and to associate these with the occurrence of PE. The data collection took place at Agios Savvas Anticancer Hospital from January, 2019 to January, 2020. The patients were also followed-up on outcomes and for the detection of PE recurrence. Data analysis was performed with the use of a comprehensive statistical analysis software.

Participants and data collection. The study participants had active cancer or suffered from cancer over the last decade and were in follow-up. Imaging diagnosis of PE was confirmed by a CTPA scan, performed using a 64-slice CT scanner (Philips Ingenuity Core 64, Integrity Medical Systems, Inc.), in accordance with the dedicated protocol, with the use of 80-100 ml iodinated intravenous contrast agent (350 mg/ml). CT images were evaluated by experienced chest radiologists who specifically searched for the presence of contrast filling defects within the pulmonary arterial tree down to a sub-segmental level. Findings consistent with acute PE are a complete filling defect (vessel size normal or dilated, eccentric filling defect with the acute angle with the artery wall, central filling defect surrounded by contrast, 'polo-mint sign' (in cross-section), which is central filling defect surrounded by contrast circumferentially and 'railway track sign' (along the long axis of the vessel). Findings consistent with old PE are a complete filling defect (vessel size normal or smaller than adjacent patent vessel), and a peripheral, crescent-shaped defect with the obtuse angle with the artery wall and web or flap (linear defect) (11). The patients were classified according to the most proximal site of occlusion as having central PE (main trunk, main pulmonary arteries and lobar branches) or peripheral PE (segmental and subsegmental branches). Unilateral or bilateral embolus cite were also noted.

For all patients, the following data were collected: i) Demographics (age and sex); ii) comorbidities (diabetes mellitus, arterial hypertension, history of smoking, depression, coronary artery disease); iii) data concerning cancer: Type of cancer, time interval between cancer diagnosis and the occurrence of PE, type of received therapy (surgery, chemotherapy, radiotherapy, or a combination) and the presence of metastases; iv) clinical signs and symptoms: Tachypnea, fever, chest pain, precordial pain, lower limb edema, fatigue, arterial pressure value and the number of patients with an incidental diagnosis of PE (asymptomatic); v) predisposing factors for PE development: Performance status, hospitalization, immobility, the presence of central venous catheter, history and type of chemotherapy administration over the past month, medical history of PE or VTE or receiving anticoagulants for any another reason; vi) laboratory data: a) Complete blood count: White blood cell, hemoglobin (Hb), hematocrit (Ht) and platelet count (PLT count); b) coagulation testing: Prothrombin time, partial thromboplastin time, international normalized ratio, fibrinogen and D-dimer levels; c) biochemical parameters: Levels of blood urea nitrogen, creatinine, total proteins, albumin; d) serum

Table I. Characteristics of the study population and cancer-related data.

Parameter	No. of patients	Percentage
Sex		
Male	38	63.3
Female	22	36.7
Smoking status (active smokers)		
Yes	12	20
No	48	80
Comorbidities		
Arterial hypertension	16	26.7
Diabetes mellitus	6	10
Coronary artery disease	4	6.7
Depression	4	6.7
No comorbidities	18	30
Type of cancer		
Lung cancer	16	26.7
Gastrointestinal cancer	14	23.3
Pancreatic	4	6.7
Stomach	2	3.3
Rectal	2	3.3
Large bowel	2	3.3
Appendix	2	3.3
Cholangiocarcinoma	2	3.3
Breast	12	20
Renal	6	10
Nasal	2	3.3
Unknown primary	6	10
Ovarian	2	3.3
Endometrial	2	3.3
Time interval between cancer diagnosis and PE occurrence		
≤6 months	38	63.3
1 month	12	20
2 months	8	13.3
5 months	6	10
6 months	12	20
>6 months	22	36.7
6-12 months	12	20
13-24 months	4	6.7
25-36 months	0	0.0
37-48 months	2	3.3
49-60 months	2	3.3
61-72 months	2	3.3
Patients who developed PE in the first year from the time of cancer diagnosis	50	3.3
Type of therapy received		
Chemotherapy	22	36.7
Surgery	6	10
Chemotherapy + surgery	14	23.3
Chemotherapy + radiotherapy	4	6.7
Chemotherapy + surgery + radiotherapy	6	10
None	8	13.3
Presence of metastases		
Yes	38	63.3
No	22	36.7

PE, pulmonary embolism.

levels of tumor markers: Carcinoembryonic antigen (CEA), CA 125, CA 19-9; e) inflammatory markers: C-reactive protein (CRP) and procalcitonin (PCT); and f) data from blood gases analysis: pH, partial pressure of oxygen, partial pressure of carbon dioxide, lactic acid and oxygen saturation; vii) radiological findings: a) CTPA: Location of obstructed branches of pulmonary arteries, the presence of pleural effusion and the presence of pulmonary metastases; b) echocardiography: Ejection fraction, dilation of right ventricle; and c) ultrasonography of the lower extremity veins: Venous thrombosis, venous insufficiency; viii) electrocardiography (ECG) findings: Basic rhythm, heart rate, the presence of abnormal findings; ix) type of therapy received for PE, outcome and re-occurrence of PE over a follow-up period of 6 months.

Statistical analysis. Data entry and analysis were performed using the SPSS statistical software (version 13.0; SPSS, Inc.). Categorical variables were summarized as the number (percentage) and continuous variables as the mean (standard deviation). The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were compared using an independent samples Student's unpaired t-test. A value of $P<0.05$ was considered to indicate a statistically significant difference. The authors consider that the statistical analysis was successful as the data collected were of good quality with no missing records and the analysis was conducted with rigorous responses to the research questions.

Results

A total of 60 cancer patients with a confirmed diagnosis of PE by CTPA were enrolled in the present study. As regards the study demographics, the majority of the cancer patients were males (38/60, 63.3%). The mean age of the patients was 61.1±7.1 years. In total, 42 patients had comorbidities. The most common comorbidity was arterial hypertension (16/10, 26.7%), while 12 patients (12/60, 20%) were active smokers (Table I).

Concerning the cancer-related data, the most common type of cancer was lung cancer (16/60, 26.7%), followed by breast cancer (12/60, 20%), renal cancer (6/60, 10%) and cancer of unknown primary, under investigation (6/60, 10%). The mean time interval between cancer diagnosis and the occurrence PE

Table II. Symptoms, signs and arterial pressure values of the study population, predisposing factors for PE, types of receiving chemotherapy and anticoagulants.

Parameter	No. of patients	Percentage
Symptomatic patients	38/60	63.3
Dyspnea	30/38	78.9
Fever	12/38	31.5
Chest pain	8/38	21
Tachypnea	6/38	15.8
Fatigue	6/38	15.8
Precordial pain	2/38	5.3
Lower limb edema	14/38	36.8
Arterial hypertension (normal range, 90-130 mmHg)		
Normal	40	66.7
>130 mmHg	14	23.3
<90 mmHg	6	10
Asymptomatic patients	22/60	36.7
Incidental finding in outpatients	14/22	63.3
Visit for investigation	2/22	9
Visit for follow-up	4/22	18
Visit for chemotherapy	6/22	27.3
Visit for surgery	2/22	9
Predisposing factors for PE		
Performance status 1,2	30	50
Performance status 3,4	30	50
Immobility >7 days	16	26.7
Hospitalization	24	40
Central venous catheter	4	6.7
History of DVT	6	10
History of PE	2	3.3
Chemotherapy received the last month	36	60
Type of chemotherapy[a]		
Platinum-based	24	40
Cisplatin	8	13.3
Carboplatin	8	13.3
Oxaliplatin	8	13.3
Abraxane	2	3.3
Doxorubicin	2	3.3
Tamoxifen	2	3.3
Lonsurf	2	3.3
Letrozole	2	3.3
Carbozanitib	2	3.3
No chemotherapy	24	40
Anticoagulants	12	20
LMWH (prophylactic)	10	16.7
LMWH (therapeutic) + acetylsalicylic acid	2	3.3
Not receiving anticoagulants	48	80
Never	46	76.7
Discontinuation 5 days prior to PE (clopidogrel)	2	3.3

[a]Not all patients received chemotherapy. DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism.

was >6 months in 22 patients (22/60, 36.7%) and <6 months in 38 patients (38/60, 63.3%), while 50 patients (50/60, 83.3%) developed PE in the first year from the time of cancer diagnosis. In total, 22 (22/60, 36.7%) had only received chemotherapy, 14 patients (14/60, 23.3%) had undergone surgical resection of the tumor and had received chemotherapy, 6 patients (6/60, 10%) had undergone surgical resection of the tumor and had received chemotherapy and radiation, and 4 patients (4/60, 6.7%) had received chemotherapy and radiation, while 8 patients (8/60, 13.3%) had not received any therapy. As

Table III. Laboratory findings of the study population.

Laboratory parameter	No. of patients (n=60)	Percentage
WBC (normal range, 4-10x$10^3/\mu$l)		
Normal	24	40
>10x$10^3/\mu$l	28	46.7
<4x$10^3/\mu$l	8	13.3
PLT count (normal range, 150-450x$10^3/\mu$l)		
Normal	42	70
>450x$10^3/\mu$l	14	23.3
<150x$10^3/\mu$l	4	6.7
Hb (normal range, 14-18 g/dl)		
<14 g/dl	60	100
Ht (normal range, 38-48 %)		
<38%	60	100
PT (normal range, 11-14 sec)		
Normal	60	100
APTT (normal range, 20-40 sec)		
Normal	58	96.7
>40 sec	2	3.3
INR (normal range, 0.8-1.25 sec)		
Normal	52	86.7
>1.25 sec	8	13.3
Fibrinogen (normal range, 200-400 mg/dl)		
Normal	16	26.7
>400 mg/dl	44	73.3
D-Dimer (normal, <0.5 μg/ml)		
>0.5 μg/ml)	60	100
Blood urea nitrogen (normal range, 15-45 mg/dl)		
Normal	54	90
>45 mg/dl	6	10
Creatinine (normal range, 0.6-1.40 mg/dl)		
Normal	44	73.3
>1.40 mg/dl	2	3.3
<0.6 mg/dl	14	23.6
Total proteins (normal range, 6.2-8.5 g/dl)		
Normal	40	66.7
<6.2 g/dl	20	33.3
Albumin (normal range, 3.5-5.2 g/dl)		
Normal	40	66.7
<3.5 g/dl	20	3.3
CRP (normal, <6 mg/l)		
Normal	14	23.3
>6 mg/l	46	76.7
PCT (normal, <0.05 ng/ml)		
Normal	12	20
>0.05 ng/ml	48	80

Table III. Continued.

Laboratory parameter	No. of patients (n=60)	Percentage
No. of elevated serum tumor markers		
1	22	45.8
2	6	12.5
3	6	12.5
pH (normal range, 7.35-7.45)		
Normal	8	13.3
>7.45	52	86.7
<7.35	0	0
pO_2 (normal range, 75-100 mmHg)		
Normal	10	16.7
>100 mmHg	2	3.3
<75 mmHg	48	80
pCO_2 (normal range, 35-45 mmHg)		
Normal	34	56.7
>45 mmHg	20	33.3
<35 mmHg	6	10
Lactic acid (normal range, 0.5-2 mmol/l)		
Normal	16	26.7
>2 mmol/l	44	73.3
Oxygen saturation (normal range, 95-100%)		
Normal	0	0
<95%	60	100

APTT, partial thromboplastin time; CRP, C-reactive protein; Hb, hemoglobin; Ht, hematocrit; INR, international normalized ratio; PCT, procalcitonin; PLT count, platelet count; PT, prothrombin time; WBC, white blood cell.

regards the presence of metastases, the majority of patients had metastases at the time of PE occurrence (38/60, 63.3%) (Table I).

More specifically, 4 patients with lung cancer were at stage IIA (T2BN0M0), 2 patients with appendix cancer were at stage IIIA (T2N1M0) and IIIB (T3N1M0), respectively, 2 patients with renal cancer were at stage II (T2N0M0 and T3N0M0), 2 patients with breast cancer were at stage IB [T2N0M0, grade 3, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor (ER)-positive and progesterone receptor (PR)-positive; and T3N2M0, grade 2, HER20positive, ER-positive and PR-positive], 1 patient with breast cancer was at stage IIB (T3N2M0, grade 2, HER2-negative, ER-negative and PR-negative), 1 patient with rectal cancer was at stage IIA (T4aN0M0), 1 patient with rectal cancer was at stage IIB (T4bN0M0), 1 patient with cholangiocarcinoma was at stage IIIA (T3N0M0), 1 patient with endometrial cancer was at stage II (T2N0M0) and 1 patient with endometrial cancer was at stage IIIB (T3bN0M0). All the other cancer patients were at stage IV (data not shown).

Table IV. Laboratory parameters with statistically significant difference between symptomatic and asymptomatic cancer patients.

Laboratory parameter	Mean value (SD)	P-value
PLT count (x10^3/μl)		
Symptomatic	268.64 (128.89)	0.014
Asymptomatic	355.46 (134.58)	
D-dimer (μg/ml)		
Symptomatic	12.78 (10.81)	0.001
Asymptomatic	3.43 (2.06)	
Albumin (g/dl)		
Symptomatic	3.61 (0.37)	0.012
Asymptomatic	3.28 (0.55)	
CEA (μg/l)		
Symptomatic	1,988.60 (4,313.63)	0.044
Asymptomatic	22.79 (48.84)	
Lactic acid (mmol/l)		
Symptomatic	1.31 (0.37)	0.001
Asymptomatic	1.9 (0.597)	

CEA, carcinoembryonic antigen; PLT count, platelet count.

A total of 38 patients (38/60, 63.3%) were symptomatic, while in 22 patients (22/60, 36.7%), PE was an incidental finding. Among the asymptomatic patients (out of the total number of patients), 8 patients (8/60, 13.4%) were hospitalized and 14 patients (14/60, 23.3%) were outpatients who visited the hospital for investigation, follow-up, chemotherapy administration or to undergo surgery. Among the asymptomatic patients, the majority of the cancer patients were females (16/22, 72.7%). Also among the asymptomatic patients, the most common type of cancer observed was breast cancer (6/22, 27.3%) and of unknown primary (6/22, 27.3%), and the majority of patients had metastases at the time of PE occurrence (14/22, 63.3%) (data not shown).

Among the symptomatic individuals, the most common symptom was dyspnea (30/38, 78.9%), followed by fever (12/38, 31.5%) and chest pain (8/38, 21%). A total of 14 patients presented with signs of lower limb edema (14/38, 36.8%). The majority of patients (40/60, 66.7%) had an arterial pressure value within the normal range (Table II).

After analyzing the predisposing factors for PE, the most common factor was chemotherapy administration over the past month (36/60, 60%). The most common type of chemotherapy used was platinum-based chemotherapy (24/60, 40%). As regards the use of anticoagulants, 48 patients (48/60, 80%) were not receiving anticoagulants, 10 patients (10/60, 16.7%) were receiving low molecular weight heparin (LMWH) and 2 patients (2/60, 3.3%) were receiving a combination of LMWH and acetylsalicylic acid due to known arterial thrombosis (Table II).

All the patients presented with lower than normal values of Hb, Ht and oxygen saturation and greater than normal D-dimer levels. A large number of patients presented with greater than normal values of fibrinogen (44/60, 73.3%), CRP (46/60, 76.7%), PCT (48/60, 80%), pH (52/60, 86.66%) and lactic acid (44/60, 73.3%) (Table III).

The mean value of the PLT count was 268.64±128.89 x10^3/μl in symptomatic patients and 355.46±134.58 x10^3/μl in asymptomatic patients; the mean value of D-dimer was 12.78±10.81 μg/ml in symptomatic patients and 3.43±2.06 μg/ml in asymptomatic patients; the mean value of serum albumin was 3.61±0.37 g/dl in symptomatic patients and 3.28±0.55 g/dl in asymptomatic patients; the mean value of serum CEA was 1988.60±4313.63 μg/l in symptomatic patients and 22.793±48.84 μg/l in asymptomatic patients; and the mean value of lactic acid was 1.31±0.37 mmol/l in symptomatic patients and 1.9±0.59 mmol/l in asymptomatic patients. The results of analysis using independent t-tests are presented in Table SI. In the Levene's test, when the significance level (sig) was >0.05, the P-value in the first row in the table for each parameter was taken into account and when the significance level (sig) was <0.05, the P-value in the second row in the table for each parameter was taken into account. There was a statistically significant difference in the mean values of the PLT count, D-dimer, albumin, CEA and lactic acid between the symptomatic and asymptomatic cancer patients with PE (P<0.05) (Table IV, and Figs. 1-3).

The majority of the cancer patients developed central PE (44/60, 73.3%). In total, 16 patients (16/60, 26.7%) had thrombosis on ultrasonography of lower extremity veins, while 8 patients (8/60, 13.3%) had a dilated right ventricle on echocardiography (Table V).

In addition, 34 patients (34/60, 56.67%) presented with sinus tachycardia on the ECG and 6 patients (6/60, 10%) presented with right bundle branch block (Table V). As regards outcomes, 8 patients (8/60, 13.3%) succumbed during hospitalization, and during the follow-up period of 6 months none of the remaining patients had a relapse of PE and all survived (Table VI). Representative images of PE are illustrated in Fig. 4.

Discussion

According to the results of the present study, the majority of the cancer patients were male, with the vast number of these patients being female in the asymptomatic group. The most common type of cancer was lung cancer, with the majority of the cases of PE occurring within the first year of cancer diagnosis, while the majority had already had metastases. The majority of the cancer patients had received chemotherapy over the past month, were not receiving anticoagulants and had central obstruction of pulmonary arteries. These factors may be considered by clinicians as additional predisposing factors for the development of PE. In addition, the present study found that 36.7% of the patients had asymptomatic PE. This finding indicates that clinicians need to be aware of this frequent complication in cancer patients, even in the absence of clinical symptoms.

Aleem *et al* (12), in their study on cancer patients who developed PE, found that the majority of the patients had symptomatic thrombosis, developed PE the during the first year after diagnosis and were at an advanced stage of cancer at the time of diagnosis. According to another study by Ohashi *et al* (13), the most common type of cancer associated with the occurrence of PE was pancreatic cancer and the majority of the patients were

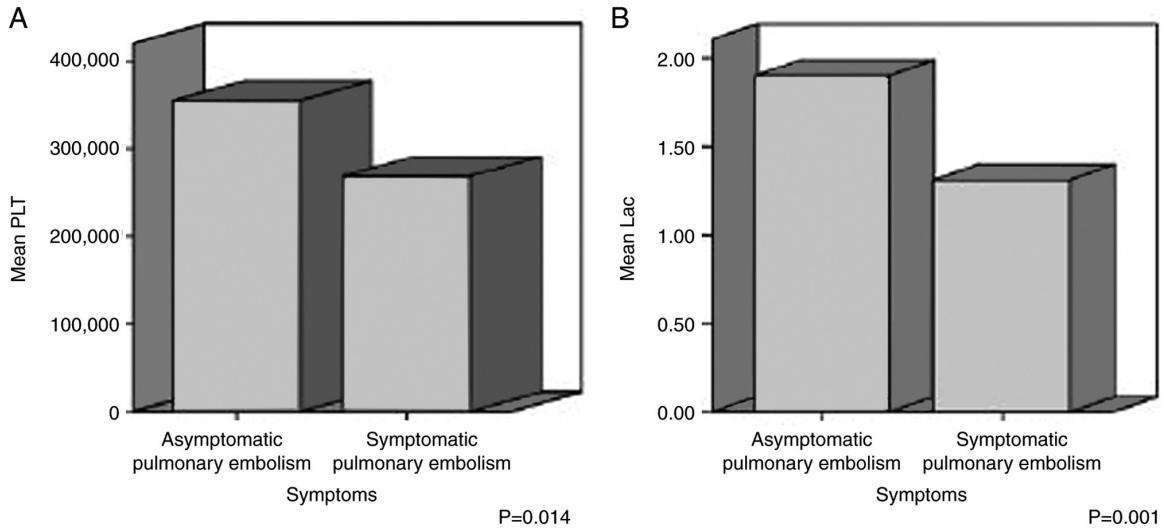

Figure 1. (A) Mean values of PLT in symptomatic and asymptomatic patients with pulmonary embolism. (B) Mean values of serum lactic acid in symptomatic and asymptomatic patients with pulmonary embolism. PLT, platelet count; Lac, lactic acid.

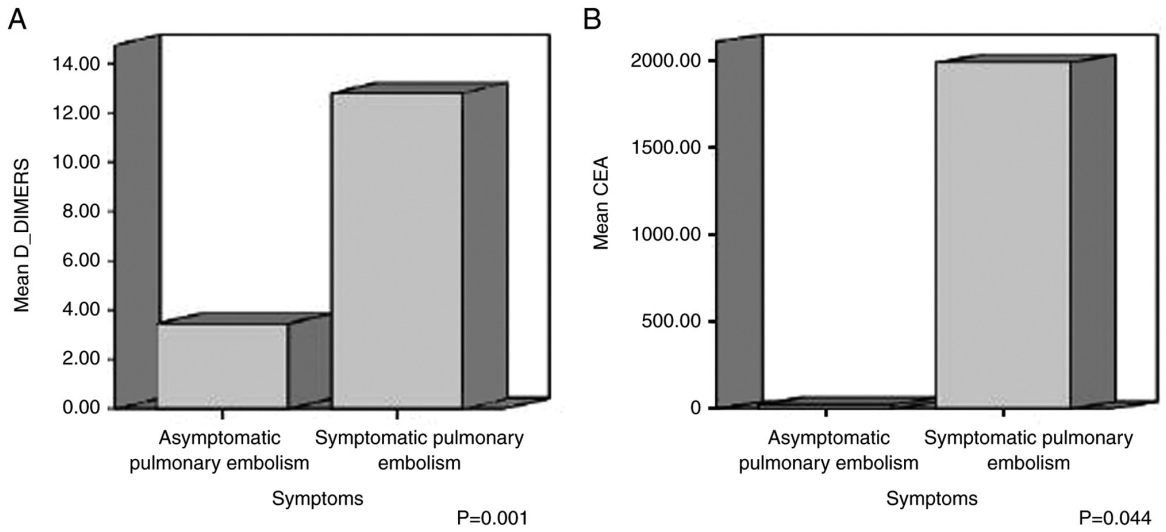

Figure 2. (A) Mean values of D-dimer in symptomatic and asymptomatic patients with pulmonary embolism. (B) Mean values of serum CEA in symptomatic and asymptomatic patients with pulmonary embolism. CEA, carcinoembryonic antigen.

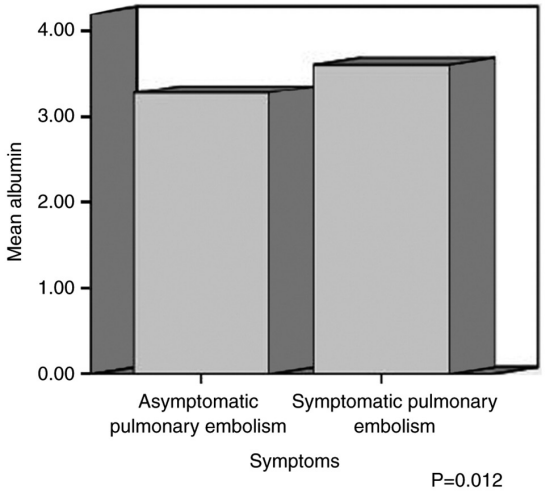

Figure 3. Mean values of serum albumin in symptomatic and asymptomatic patients with pulmonary embolism.

at an advanced stage when diagnosed with PE. Furthermore, Meyer *et al* (14), in their study on cancer patients with PE, found that 3,36% had asymptomatic PE. The most common type of cancer was prostate cancer, followed by hepatobiliary carcinoma and pancreatic cancer (14). In another study by Silva *et al* (4), it was found that the majority of the cancer patients who developed PE were female and the most common types of cancer were colorectal and lung cancer, most of which had metastases or had received chemotherapy. In the same study, PE was an incidental finding in 69.4% of the patients (4).

In their study, Myat Moe *et al* (15) found that the incidence of asymptomatic PE among cancer patients was low (1.6%); the majority of patients were female and the most common types of cancer observed in these patients were lung, breast and colorectal cancer, which is most likely due to the frequency of imaging (15). Furthermore, in the study by Abdel-Razeq *et al* (16), it was demonstrated that the most

Table V. CTPA, ultrasonography of the lower extremity veins, echocardiography and electrocardiography findings.

CTPA	No. of patients	Percentage
Location of obstructed branches of pulmonary arteries		
Central	44	73.3
Main pulmonary arteries and lobar branches	44	73.3
Lateral	24	40
Bilateral	20	33.3
Peripheral	16	26.3
Segmental branches	14	23.3
Subsegmental branches	2	3.3
Pleural effusion	20	33.3
Pulmonary metastases	20	33.3
Ultrasonography of the lower extremity veins		
Thrombosis	16	26.7
Symptomatic	14	23.4
Asymptomatic	2	3.3
Venous insufficiency	2	3.3
No abnormal findings	42	70
Echocardiography		
Normal EF	60	100
Dilation of right ventricle	8	13.3
Electrocardiogram findings		
Sinus rhythm	60	100
RBBB	6	10
Sinus tachycardia	34	56.7
Normal rhythm (60-100 pbm)	26	43.3

CTPA, computed tomography pulmonary angiogram; EF, ejection fraction; RBBB, right bundle branch block.

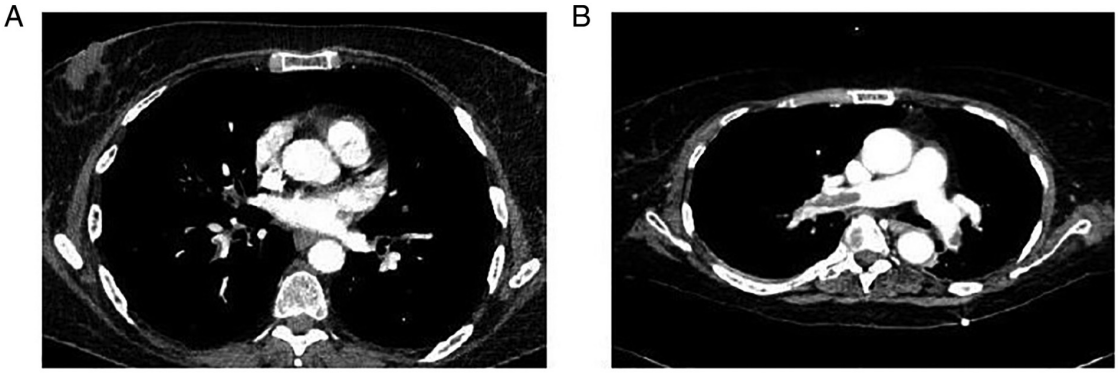

Figure 4. (A) Low density filling defects representing acute pulmonary embolism in a segmental branch of the right lower lobe pulmonary artery in a 52-year old female patient with breast cancer. (B) Low density filling defects representing acute pulmonary embolism in both right and left main artery in a 60-year-old female patient with ovarian cancer.

frequent types of cancer in cancer patients with asymptomatic PE were gastric, lung, colorectal and lymphomas. Similar to the findings of the present study the majority of the asymptomatic patients were female and most of the patients (77%) had already developed metastases at the time of PE diagnosis (16). In addition, in a review article by van Es *et al* (17), the reported incidence of incidental PE in cancer patients was 1-5%. This finding is in contrast to the results of the present study.

Another notable finding of the present was a statistically significant difference in the mean values of PLT counts, D-dimer, albumin, CEA and lactic acid between the symptomatic and asymptomatic cancer patients with PE, with greater values of PLT counts and lactic acid, and lower values of

Table VI. Type of anticoagulation received for the treatment of pulmonary embolism and outcomes.

Therapy and outcome	No. of patients	Percentage
Anticoagulation therapy received during hospitalization		
Tinzaparin	44	73.3
Enoxaparin	16	26.7
Mortality during hospitalization	8	13.3
Tinzaparin	8	13.3
Enoxaparin	0	0
Anticoagulation therapy received following discharge		
Tinzaparin	34	65.4
Enoxaparin	16	30.8
DOAC	2	3.8
Follow-up	0	0
Relapse	0	0
Mortality	0	0

DOAC, direct-acting oral anticoagulant.

D-dimer, CEA and albumin observed in asymptomatic cancer patients. These parameters may guide clinicians to suspect PE even in asymptomatic patients.

To date, several PE clinical scoring systems are used to calculate the pretest probability of PE. Among the most common scoring systems are the PERC score, the Wells score and the Geneva score (18-20). The PERC score suggests that when a patient is <50 years of age, has a pulse <100 bpm, an oxygen saturation >94%, no unilateral leg swelling, no hemoptysis, no recent surgery and no oral hormone use, the pretest probability of PE is likely to be very low (18). The Wells score is used to guide additional investigations and management using medical history data, including a history of cancer and clinicals signs of VTE to determine whether PE is likely or unlikely (19). In addition, the Geneva score is used to calculate the pretest probability of PE by using patient risk factors, such as an age >65 years, surgery, previous DVT and a history of cancer, and clinical signs and symptoms (20).

CEA has been reported to be associated with an increased risk of developing VTE in patients with pancreatic, colorectal and ovarian cancer (21), and is related to PE in patients with lung cancer, with a positive correlation with D-dimer values (22). To the best of our knowledge, the present study is the first to describe low levels of CEA as a potential biomarker for detecting PE in asymptomatic cancer patients.

Lactic acid has been reported to be associated with a high risk of mortality and adverse outcomes among patients with PE (23), and an increased in-hospital mortality in patients with acute PE (24). Furthermore, 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 (25). In a recent study, Ząbczyk *et al* (26) reported that increased lactic acid levels were associated with increased neutrophil extracellular trap (NET) formation and prothrombotic fibrin clot features, with impaired plasma fibrinolytic potential in patients with acute PE. However, cancer patients were excluded from that study (26). Although there are several reports regarding the role of lactic acid in patients with PE, 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.

Low levels of serum albumin have been shown to be associated with massive PE (27) and an increased risk of VTE development in acutely ill hospitalized patients (28). Moreover, decreased serum albumin levels have been found to be significantly associated with an increased risk of VTE and mortality in cancer patients (29). Of note, Li *et al* (30) reported that low serum levels of albumin were independently associated with the development of asymptomatic PE. According to the present study, low levels of serum albumin may be a potential biomarker for detecting PE among asymptomatic cancer patients.

In their study on cancer patients, Ali *et al* (31) found that cancer patients with asymptomatic PE had increased D-dimer levels similar to those found among cancer patients with symptomatic PE, indicating that elevated D-dimer levels should raise the suspicion of PE in asymptomatic cancer patients. In the present study, D-dimer levels were significantly lower in asymptomatic cancer patients with PE as compared to symptomatic patients. The inverse association of D-dimer levels with PLT counts may be explained by the local consumption of platelets due to a thrombotic state (32). According to the present study, another potential biomarker for detecting PE among asymptomatic cancer patients is the increased PLT count.

In the present study, the in-hospital mortality rate was 13.3%, while during a follow-up period of 6 months, there was no relapse or mortality observed in the patients. In the study by Silva *et al* (4), the mortality rate at 30 days associated with PE in cancer patients was 7.5%. In another study, the reported overall 30-day mortality rate in a large cohort of cancer patients with PE was 14% (33). Furthermore, a mortality rate of 22.1% was reported in a study on cancer patients with PE at the end of follow-up period (34).

To the best of our knowledge, the present study is to one of a limited number of studies investigating the characteristics and outcomes of cancer patients who developed PE in Greece. The strong point of the study was its cross-sectional design, accompanied by reliable follow-up and outcome data. However, the study has some limitations. One limitation of the research is the relatively small sample size of the patients. 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 majority of the cancer patients who developed PE were male. The most common type of cancer observed was lung cancer, with the vast number of cases of PE occurring within the first year from cancer diagnosis, while the majority of the patients had already developed metastases. The majority of the cancer patients had received chemotherapy over in past month, were not receiving anticoagulants and had central obstruction of pulmonary arteries. A large proportion had asymptomatic PE. Clinicians may consider these factors as additional predisposing factors for the development of PE. A great proportion had asymptomatic PE. This finding suggests

that even in the absence of clinical signs and symptoms, doctors need to be aware of this common consequence in cancer patients. The in-hospital mortality rate was 13.3% and no relapse or mortality were noted during the follow-up period of these patients. Increased levels of lactic acid and increased number of PLTs, as well as low serum levels of CEA, albumin and D-dimer, may be potential biomarkers for asymptomatic PE among cancer patients. These parameters may guide oncologists to suspect PE even in asymptomatic patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SC, VEG and MM conceptualized the study. CD, PS, NT and PP obtained the data and prepared the tables. EG, PG and DT obtained the data and prepared the figures. AG, GAL, AT were involved in the design of the study and prepared the draft of the manuscript. VEG and SC wrote and prepared the draft of the manuscript. DAS and GK analyzed the data and provided critical revisions. VEG and SC confirm the authenticity of all the raw data. All authors contributed to manuscript revision and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approval for the present study was obtained from the Research Ethics Committee of Agios Savvas Hospital (protocol no. 8034/1-12-18). The study was in line with the declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Written informed was obtained from all the patients prior to enrollment.

Patient consent for publication

Written informed was obtained from the patients for publication of the data. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The author authors declare that they have no competing interests.

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