

Malignancy and Pulmonary Thromboembolism: Comparison of Symptomatic Cases with the Incidental Ones

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ABSTRACT

Objectives: The use of advanced techniques of computed tomography (CT) was resulted in increased incidentally detected pulmonary embolism in oncology patients undergoing routine cancer staging CT scans. The aim of this study was to compare the symptomatic and incidental pulmonary emboli cases in oncologic patients.

Methods: The medical data of the patients diagnosed with pulmonary embolism (ICD: I.26) and had an underlying malignancy were evaluated retrospectively from the hospital records between the years of 2009 and 2013. Right ventricle dilatation findings were evaluated from the thorax CT.

Results: There were 38 women (44.2%), 48 men (55.8%), totally 86 patients. The mean age was 61.7 ± 11.9 years and the median duration of follow-up was six months. The most common underlying malignancies were gastrointestinal (29.4%), lung (22.4%), genitourinary (21.2%) and breast cancers (10.6%). Pulmonary thromboembolism was diagnosed incidentally on routine control thorax CT in thirty-nine of the cases (45.3%). When the incidental cases compared to symptomatic ones; no statistically significant difference was found with respect to the type of malignancy, chemotherapy history, presence of metastasis and evidence of septum flattening on thorax CT. The presence of bilaterally thrombus was found as increased in symptomatic cases compared to incidental ones and the difference was statistically significant ($p = 0.026$). It was found that the RV/LV ratio was significantly higher in symptomatic cases ($p = 0.03$).

Conclusion: A considerable number of pulmonary thromboemboli episodes could be asymptomatic in malignant patients. It is suggested that the sub-massive clinical course and preserved right ventricle functions could be the reason of asymptomatic events.

Keywords: Malignancy, pulmonary thromboemboli, incidental

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INTRODUCTION

Venous thromboembolism (VTE) is a clinical entity includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Most important recognized risk factors of VTE are cancer and its treatment (1). It is known that the incidence of venous thromboembolism in oncologic patients higher than without malignancy, also the prognosis is worse in oncologic patients (2–4). Oncologic patients undergo routine imaging studies much more than others. These imaging procedures are used for diagnosis of the disease, extent of the disease (staging) and assessment of response to cancer therapy (1). The improvement of quality of techniques, use of multi-detector CT scanners and widespread use of computed tomography (CT) in cancer patients resulted in increased incidentally detected pulmonary embolism in oncology patients undergoing routine cancer staging CT scans (1, 5).

Incidental pulmonary embolism is defined that pulmonary embolism detected in thorax CT taken for malignancy staging or follow-up of treatment without clinic suspicion of pulmonary embolism (6). These incidentally detected VTEs are variously referred to in the literature as incidental, asymptomatic, unexpected or unsuspected VTE (7). A recent guidance paper by the Hemostasis and Malignancy Subcommittee of the International Society on Thrombosis and Hemostasis provided recommendations regarding this terminology (now termed incidental) and reporting of incidental VTE for clinical trials (8).

While the association between cancer and symptomatic venous thromboembolism (VTE) is well known, the incidence and risk factors for incidental VTE in cancer patients remain unclear (9). The aim of this study was to compare the symptomatic and incidental pulmonary emboli cases in oncologic patients.

MATERIAL AND METHOD

In a retrospective, single-center study from 2009 to 2013, the medical data of the patients diagnosed with pulmonary embolism and malignancy at outpatient or inpatient clinics of Kocaeli University School of Medicine were evaluated. The International Code of Diseases (ICD-10) was used to defining the patients. There was 246 patients with the code of pulmonary embolism (ICD: I.26). One hundred twenty eight of them had a history of malignancy. But the radiologic imaging's of the forty two patients who were referred to our clinic with for diagnosis and follow-up from external hospital were not available and they were excluded. Totally 86 patients diagnosed with pulmonary embolism and any of malignancy were included in the study. The demographic characteristics, duration of the disease, type of malignancy, presence of the metastasis, history of chemotherapy were recorded.

The thorax computed tomographies of the all included patients were re-evaluated by an experienced Radiologist. The localization of the thrombus, evidence of septum flattening, and right ventricle dilatation findings were recorded. The reasons of request thorax computed tomography (CT) were shown in (Fig. 1). The categories of 1, 2 and 3 were accepted as without suspicion of PTE and the category 4 accepted as suspicion of PTE.

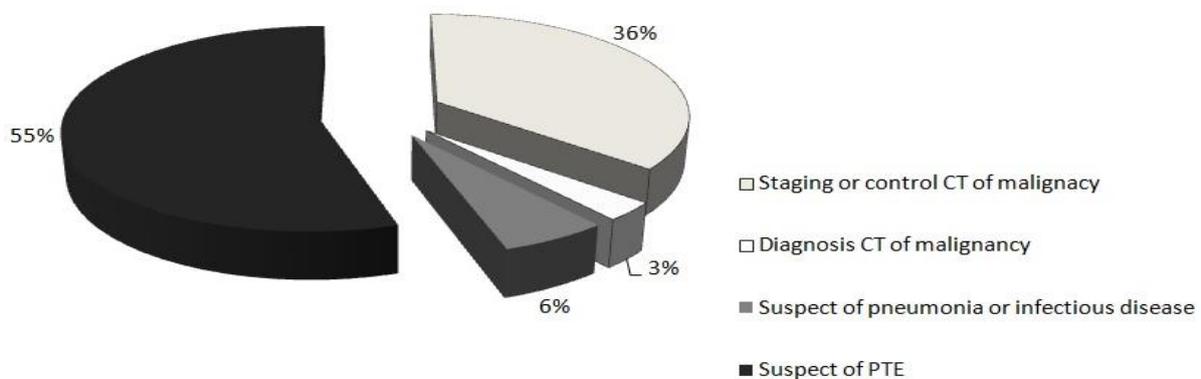


Figure. 1: The reason of request thorax CT

Statistical analysis

Statistical Package for Social Sciences (SPSS.16) was used for the statistical analysis of the study. The continuous variables were presented as mean and standard deviation. The categorical variables were presented as percentages. Chi-squared test (X^2) test was used for comparing categorical variables. The comparison of continuous variables was analysed by *t*-test. A *p*-value of < 0.05 was considered significant.

RESULTS

There were 38 women (44.2%), 48 men (55.8%), totally 86 patients. The mean age of the patients was 61.7 ± 11.9 years. And the median duration of follow-up was six months. It was found that 66.3% of the patients had distant organ metastasis and 75.6% of them had chemotherapy history. The thrombus was bilaterally in 60.2% of the patients and it was located in main pulmonary artery 40% of the patients. The demographic characteristics of the patients were shown in (Table.1). Thirty-nine of the cases (45.3%) had incidentally detected pulmonary thromboembolism on routine control thorax CT.

Table.1: Demographic characteristics of the patients

		n(%)
Age (years)	61.7 ± 11.9 (Min:30, Max:82)	
Gender	Female: 38	38 (44.2%)
	Male: 48	48 (55.8%)
Metastasis	(+)	55 (66.3%)
	(-)	28 (33.7%)
History of chemotherapy	(+)	65 (75.6%)
	(-)	21 (24.4%)
Hospitalization	Outpatient	31 (36%)
	Inpatient	55 (64%)
Thrombus localization (%)	Bilaterally	60.2
	Right	24.1
	Left	15.7
Involvement (%)	Main pulmonary artery	40
	Lobar arteries	50.6
	Segmental arteries	9.4

The most common underlying malignancies were gastrointestinal (29.4%), lung (% 22.4%), genitourinary (21.2%) and breast cancers [10.6%] (Fig. 2).

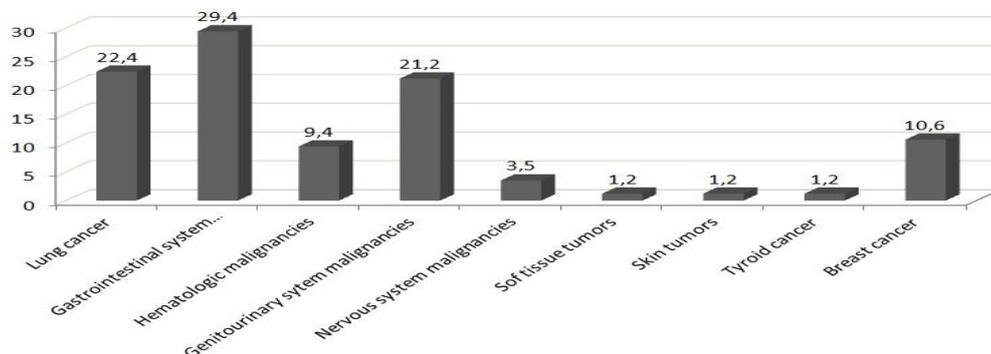


Figure. 2: The distribution of malignancies accompanying with pulmonary thromboembolism (%).

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When the incidental cases compared to symptomatic ones; no statistically significant difference was found with respect to the type of malignancy. However, there was a non-significant increase of incidental PE cases in malignancies such as lung cancer, gastrointestinal system malignancies and breast cancer [$p > 0.05$] (Fig. 3).

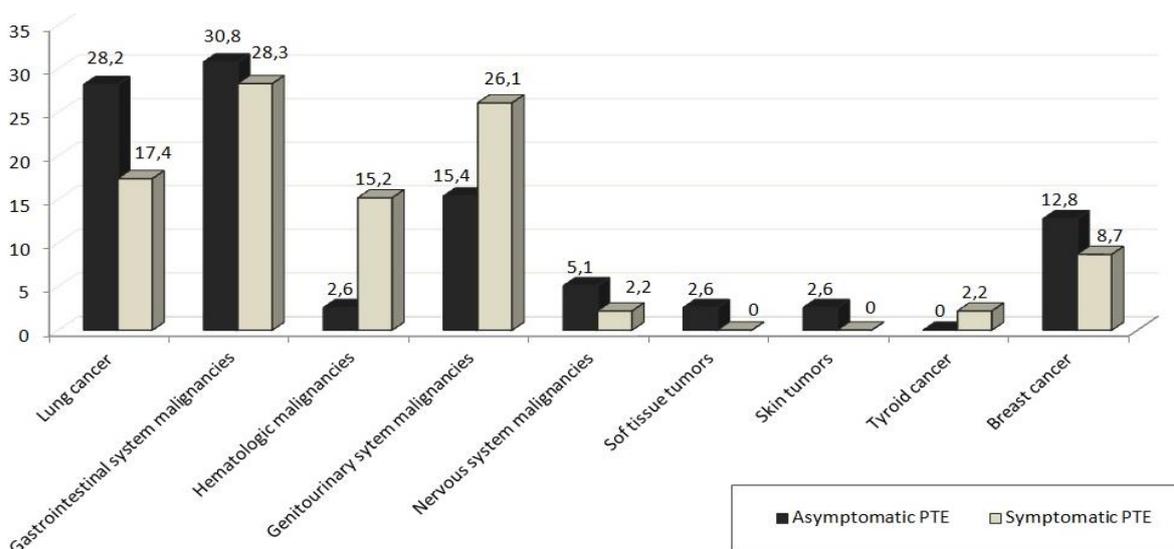


Fig. 3: The distribution of malignancies according to asymptomatic and symptomatic PTE cases (%).

When the incidental cases compared to symptomatic ones; no statistically significant difference was found with respect to the chemotherapy history and presence of metastasis ($p > 0.05$).

The presence of thrombus in main pulmonary artery was found as increased in symptomatic cases compared to incidental ones however the difference was not statistically significant. The bilaterally involvement was detected in 73.3% of symptomatic cases and 44.7% of asymptomatic cases and the difference was statistically significant ($p = 0.026$).

The right ventricle dilatation findings including mean diameters of main pulmonary artery, left and right ventricle were shown in Table.2.

Table. 2: The right ventricle dilatation findings in Thorax CT

Diameters (mean)	Asymptomatic PE	Symptomatic PE	<i>p</i>
Main pulmonary artery	26.1 ± 4.5	27.7 ± 4.2	0.39
Right ventricle	39.4 ± 6.98	41.04 ± 7.3	0.3
Left ventricle	39.5 ± 7.1	35.3 ± 7.2	0.009

The mean diameters of right ventricle and main pulmonary artery were higher in symptomatic cases but the difference was not statistically significant ($p > 0.05$). However, there was a significant decrease of mean left ventricle diameter in symptomatic cases than incidental cases ($p = 0.009$). Also it was found that the right ventricle/left ventricle (RV/LV) ratio was significantly higher in symptomatic cases ($p = 0.03$) [Fig. 4]. When incidental cases compared to symptomatic ones; no statistically significant difference was found with respect to evidence of septum flattening on thorax CT ($p = 0.2$).

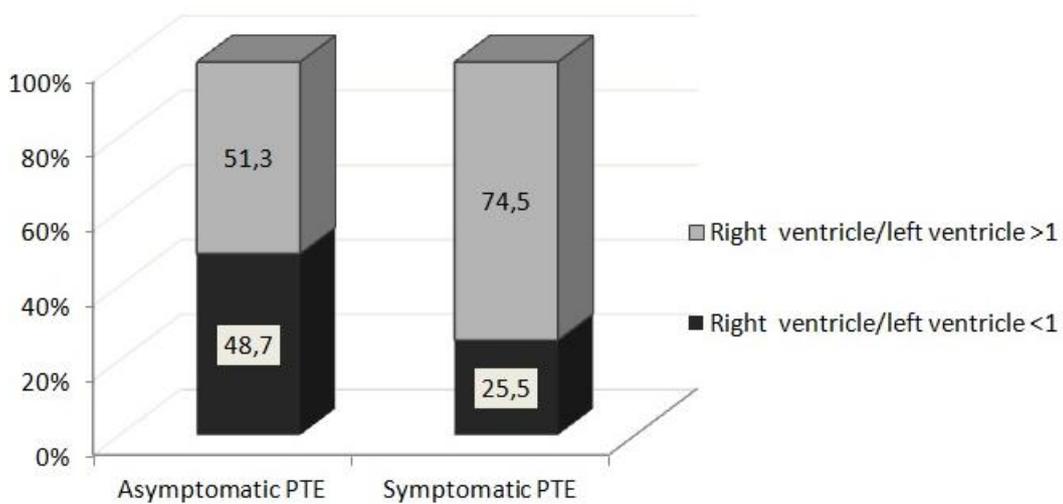


Fig. 4: The right ventricle dilatation findings between asymptomatic and symptomatic PTE cases.

DISCUSSION

It was found that nearly half of pulmonary thromboembolism episodes could be asymptomatic (45%) in malignant patients. The presence of findings such as bilaterally embolus, decreased left ventricular diameter and increased right ventricle / left ventricle ratio was higher in symptomatic PE cases than incidental cases. However, no statistically significant difference was found with respect to chemotherapy history, presence of metastasis and the type of malignancy.

Venous thromboembolism is a frequent complication of cancer due to hypercoagulable state (10). As one of the VTEs, pulmonary embolism is a common cause of mortality and morbidity in oncologic patients (6). Incidence of pulmonary embolism range from 0.13% to 8.65% in cancer patients (6, 11). The cases of pulmonary embolism may be symptomatic with the cardinal symptoms of dyspnea and chest pain or can be detected incidentally without symptoms. While the association between cancer and symptomatic venous thromboembolism (VTE) is well established, the incidence and risk factors of incidental VTE in cancer patients remain unclear (9). The reported incidence of incidentally detected PE ranges from 1% to 5% (3, 7, 12, 13). However, higher incidental PE rates have been reported among hospitalized patients and oncologic patients (7).

It was reported that most related malignancies with thrombosis were pancreas, lung and primary unknown adenocarcinomas in many studies (14). Also pulmonary embolism was a frequent unsuspected finding in staging examinations: particularly in patients with malignancies of the ovary, brain and pancreas (6). The most accompanying malignancies were ovary, brain and pancreas carcinomas in patients with VTE in Levitan *et al* study (15). However, Sorenson *et al* reported that underlying malignancies were lung (17%), pancreas (10%), colon/rectum (8%), kidney (8%) and prostate [7%] (16). The most accompanying malignancies were as follows;

gastrointestinal system malignancies (29.4%), lung cancer (22.4%), genitourinary malignancies (21.2%) and breast cancer (10.6%) in this study. The distribution of the malignancies was different in our study since the malignancies classified according to systems not to organs. Furthermore lung, gastrointestinal and breast cancers have a tendency to asymptomatic clinical course than other malignancies. But this difference was not statistically significant.

Incidental pulmonary embolism were comprised nearly 29–50% of all pulmonary embolism cases in oncologic patients (6, 17, 18). Menapace *et al* reported that incidental events were comprised 33.3% of PEs in pancreatic cancer patients (17). A total of 42% of the in lung cancer patients had clinically unsuspected PE (19). The highest rates of incidental PE were detected in Bach *et al* study, (a half of all PE patients) and in our study with a rate of 45.3%. It was thought that these higher rates of incidental PE might be related with study population including different types of malignancy.

It is known that advanced age, metastatic disease and chemotherapy are the risk factors of VTE (2, 12, 19, 20). The role of risk factors such as age, gender, presence of metastasis and history of chemotherapy on incidental PE were also evaluated in many studies (6, 19, 21).

Sahut *et al* reported that advanced age was associated with unsuspected PE (22). In contrast to this study, patients with incidental PE were similar with symptomatic PE regarding age and gender distribution (21). Bach *et al* reported that age and gender had no influence on PE risk and embolus burden (6). We also did not find a difference of age or gender between the symptomatic and incidental cases.

Pulmonary embolism was more prevalent among patients with metastatic disease (7% versus 2%, $p = 0.007$) and in patients who had received recent chemotherapy [11% versus 3%, $p = 0.008$] (12). Also, it was suggested that recent chemotherapy was associated with

unsuspected PE (22). Di Nisio *et al* suggested that half of the incidental VTE occurred in the first 3–6 months of chemotherapy and the presence of metastases and chemotherapy increased the risk up to three-fold (9). However, suspected and unsuspected PE did not differ in presence of metastatic disease at the time of PE in Shinagareet *et al* study (19). In our study 66.3% of the patients had metastatic disease and 76.3% of them history of chemotherapy at the time of PE diagnosis. But when the incidental cases compared to symptomatic ones; no statistically significant difference was found with respect to the chemotherapy history and presence of metastasis. This might be explained by a significant portion of the study population had histories of metastases and chemotherapy.

When evaluating the location of thrombus, it was found 7.7% of the patients had thrombus in main pulmonary artery, 14.6% of them in right/left pulmonary arteries, 28.5% of them in lobar arteries, 49.2% of them in segmental/sub segmental arteries (23). Another study from Turkey revealed that 2.4% of the patients had thrombus in pulmonary trunchus, 12.3% of them in right/left pulmonary arteries, 57% of them in lobar arteries, 28.3% of them in segmental/sub segmental arteries (24). The forty per cent of the cases had involvement of main pulmonary artery and 50.6% of them had lobar arteries involvement in our study. Shinagare suggested that suspected PE more commonly involved main/lobar pulmonary arteries while unsuspected PE more frequently involved of segmental arteries (19). The location of thrombus in main pulmonary artery was found as increased in symptomatic cases compared to incidental ones in our study; however the difference was not statistically significant. They were both retrospective studies, but Shinagare's study population included only patients with lung cancer while our study population covered all of the malignancies. This might be explanation of non-significant difference.

In a retrospective study it was shown that 70.7% of the PE cases were bilaterally involved (25). As similar, we found that 60.2% of the PE cases had bilateral involvement. And there was a significant difference of bilateral involvement among the groups (73.3% of symptomatic cases; and 44.7% of incidental cases; $p = 0.026$).

The use of computed tomography pulmonary angiography (CTPA) in the diagnosis of pulmonary embolism (PE) has increased as a result of advances in technology. Computed tomography pulmonary angiography has become the first diagnostic choice for imaging of pulmonary vasculature when PE is suspected in routine clinical practice (26). Sensitivity, specificity and positive predictive values of computed tomography pulmonary angiography (CTPA) were respectively 87.5%, 95.3% and 87.5% in detection of right ventricle dysfunction (27). It was reported that $RV/LV > 1$ in CTPA could be helpful to demonstrate right ventricle dysfunction (28). In a retrospective study evaluating CTPAs of the 431 patients, the mortality was found 15.6% in patients with $RV/LV > 0.9$ while it was 7.7% in patients with $RV/LV < 0.9$ (29). Nural *et al* also found that right ventricle diameter and RV/LV ratio were higher in patients with massive pulmonary embolism than patients with normal blood pressure (30). The results of our study including decreased left ventricle ratio and increased RV/LV ratio in symptomatic patients are seemed to support the literature.

Recent data suggested that cancer patients with unsuspected PE had similar mortality rates with symptomatic pulmonary embolism (5, 22). When adjusted for tumour stage and performance status, six-month mortality did not differ between patients with UPE and patients without PE (22). So, current guidelines recommend using the same approach to type and duration of anticoagulation as is used for patients with suspected PE. Among cancer patients the bulk of available data suggests that incidental PE is associated with recurrent venous thromboembolism

(VTE) and, when symptomatic, may adversely impact survival (7). Our incidentally detected patients had also anticoagulant therapy as same as symptomatic cases, too.

The limitations of our study were relatively limited numbers of the patients and retrospective study design. We defined a study protocol for avoiding information bias. The diagnoses of the patients were confirmed by evaluating both medical data and radiologic imaging. Thorax computed tomographies were also re-evaluated by an experienced radiologist for preventing bias.

In conclusion, a considerable number of pulmonary thromboembolism episodes could be asymptomatic in malignant patients. Therefore, pulmonary vasculature should be evaluated carefully in every chest imaging in oncologic patients. It is suggested that the sub-massive clinical course and preserved right ventricle functions could be the reason of asymptomatic events.

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