ORIGINAL ARTICLE

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

S Argun Baris[1], T Onyilmaz[2], S Gumustas[3], HI Ada[3], D Cabuk[4], I Basyigit[1], H Boyaci[1], F Yildiz[1]

ABSTRACT

Objective: *The use of advanced techniques of computed tomography (CT) has 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 their hospital records between the years of 2009 and 2013. The results of their right ventricle dilatations were evaluated from the thorax CT.*

Results: *There were 38 women (44.2%) and 48 men (55.8%), totalling 86 patients. Their mean age was 61.7 ± 11.9 years and the median duration of their follow-up was 6 months. Their most common underlying malignancies were gastrointestinal (29.4%), lung (22.4%), genitourinary (21.2%) and breast cancers (10.6%). Their pulmonary thromboembolism was diagnosed incidentally on routine control thorax CT in 39 of the cases (45.3%). When the incidental cases were compared with the symptomatic ones, no statistically significant difference was found with respect to the type of malignancy, history of chemotherapy, the presence of metastasis and evidence of septum flattening on the thorax CT. The presence of bilateral thrombus was found to be increased in the symptomatic cases compared with the incidental ones and the difference was statistically significant (*p *= 0.026). It was found that the right ventricle/left ventricle ratio was significantly higher in symptomatic cases (*p *= 0.03) than in the incidental ones.*

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

Keywords: Incidental, malignancy, pulmonary thromboemboli

INTRODUCTION

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

From: [1]Department of Pulmonary Diseases, Kocaeli University School of Medicine, Kocaeli, Turkey, [2]Department of Pulmonary Diseases, Mardin Government Hospital, Mardin, Turkey, [3]Department of Radiology, Kocaeli University School of Medicine, Kocaeli, Turkey and [4]Department of Medical Oncology, Kocaeli University School of Medicine, Kocaeli, Turkey.

Correspondence: Dr SA Baris, Department of Pulmonary Diseases, Kocaeli University School of Medicine, Umuttepe, Kocaeli, Turkey. Email: serapargun2002@yahoo.com

 DOI: 10.7727/wimj.2015.227

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

While the association between cancer and symptomatic 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 PE cases in oncologic patients.

SUBJECTS AND METHODS

In a retrospective, single-centre study from 2009 to 2013, the medical data of the patients diagnosed with PE and malignancy at the outpatient and the inpatient clinics of Kocaeli University School of Medicine were evaluated. The International Code of Diseases Tenth Revision (ICD-10) was used to defining the patients. There were 246 patients with the code of PE (ICD: I.26). Of those, 128 had a history of malignancy. However, the radiologic imagings of the 42 patients who were referred to our clinic for diagnosis and follow-up from the external hospital were not available and they were excluded. In all, 86 patients who were diagnosed with PE and any of malignancy was included in this study. Their demographic characteristics, duration of the disease, type of malignancy, presence of the metastasis, and the history of chemotherapy were recorded.

The thorax CTs of all the sampled patients were re-evaluated by an experienced radiologist. The localization of the thrombus, the evidence of septum flattening and the right ventricle (RV) dilatation findings were recorded. The reasons of request thorax CT are shown in Fig. 1. Categories 1, 2 and 3 were accepted as without the suspicion of pulmonary thromboembolism (PTE) and category 4 was accepted as suspicion of PTE.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS 16, IBM Corp., Armonk, NY, USA) was used for the statistical analyses of this study. The continuous variables were presented as means and standard deviations. The categorical variables were presented as percentages. The Chi-square test was used for comparing the categorical variables. The comparisons of the continuous variables were analysed using the *t*-test. A p-value of < 0.05 was considered as statistically significant.

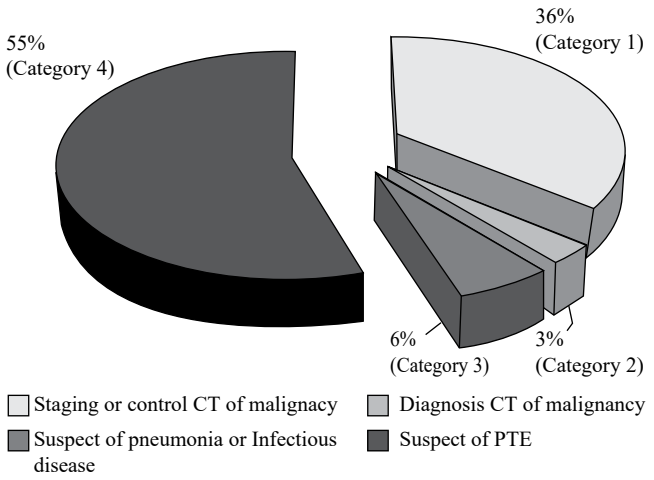

Fig. 1: The reasons of request thorax computed tomography (CT).

RESULTS

There were 38 women (44.2%), 48 men (55.8%) and overall 86 patients. The mean age of the patients was 61.7 ± 11.9 years and the median duration of their follow-up was 6 months. It was found that 66.3% of the patients had distant organ metastasis and 75.6% of them had history of chemotherapy. The thrombus occurred bilaterally in 60.2% of the patients and it was located in the main pulmonary artery of 40% of the patients. The demographic characteristics of the patients are shown in Table 1. Thirty-nine cases (45.3%) had incidentally been detected to have PTE on their routine control thorax CT.

Table 1: Demographic characteristics of the patients

		n (%)
Age (years)	61.7 ± 11.9 (minimum: 30, maximum: 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).

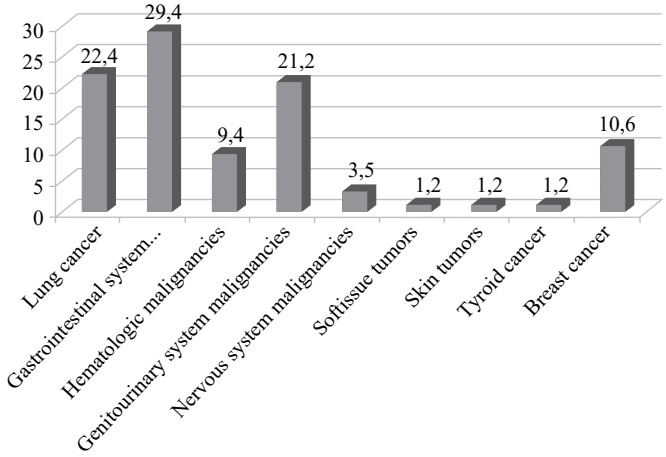

Fig. 2: The distributions of the malignancies accompanying the pulmonary thromboembolism (%).

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

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

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

The RV dilatation findings including mean diameters of main pulmonary artery and the left and the RVs are shown in Table 2.

Table 2: The right ventricle dilatation findings in thorax CT

Diameters (mean)	Asymptomatic PE	Symptomatic PE	*p*
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

PE = pulmonary embolism

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

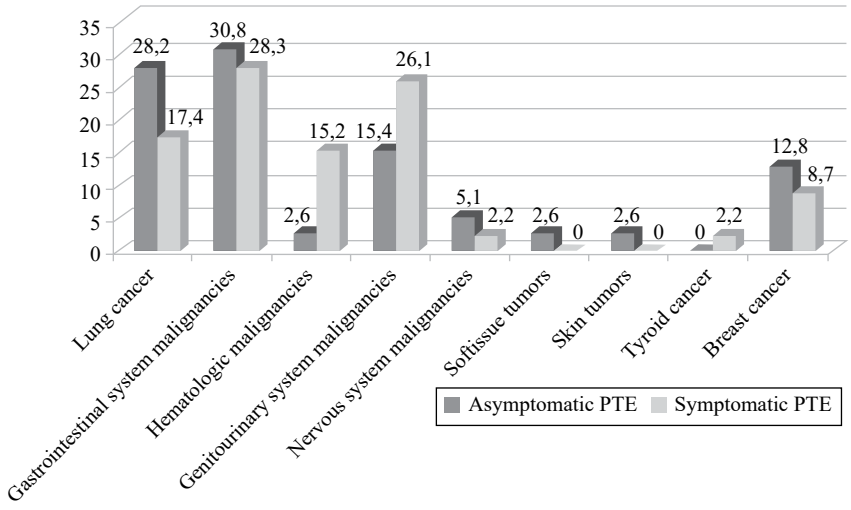

Fig. 3: The distribution of malignancies according to asymptomatic and symptomatic PTE cases (%). PTE = pulmonary thromboembolism.

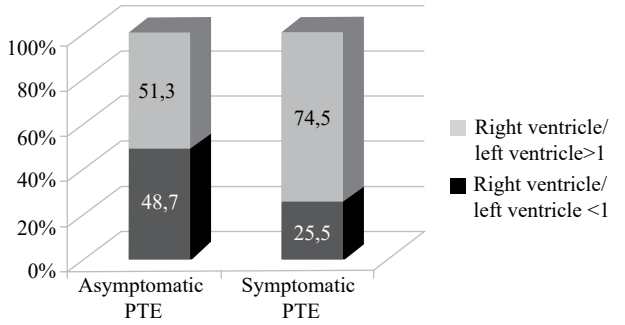

Fig. 4: The right ventricle dilatation findings between the asymptomatic and the symptomatic PTE cases. PTE = pulmonary thromboembolism.

DISCUSSION

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

Venous thromboembolism is a frequent complication of cancer due to the hypercoagulable state (10). As one of the VTEs, PE is a common cause of mortality and morbidity in oncologic patients (6). The incidence of PE ranges from 0.13% to 8.65% in cancer patients (6, 11). The cases of PE may be symptomatic with the cardinal symptoms of dyspnoea and chest pain or can be detected incidentally without symptoms. While the association between cancer and symptomatic VTE is well established, the incidence and the 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 had been reported among hospitalized patients and oncologic patients (7).

It was reported that most related malignancies with thrombosis were the pancreas, the lung and the primary unknown adenocarcinomas in many studies (14). Also, PE was a frequent unsuspected finding in staging examinations, particularly in the patients with malignancies of the ovary, the brain and the pancreas (6). The most accompanying malignancies were ovary, brain and pancreas carcinomas in the patients with VTE in Levitan *et al* study (15). However, Sørensen *et al* reported that underlying malignancies were the lung (17%), the pancreas (10%), the colon/rectum (8%), the kidney (8%), and the prostate (7%) (16). In this study, most accompanying malignancies were as follows: gastrointestinal system malignancies (29.4%), lung cancer (22.4%), genitourinary malignancies (21.2%) and breast cancer (10.6%). The distribution of the malignancies was different in our study because the malignancies were classified according to systems and not according to organs. Furthermore, lung, gastrointestinal and breast cancers have a tendency to follow the asymptomatic clinical course than other malignancies. However, this difference was not statistically significant.

The incidental PE constituted nearly 29%–50% of all the PE cases in oncologic patients (6, 17, 18). Menapace *et al* reported that incidental events accounted for 33.3% of the PEs in the pancreatic cancer patients (18). A total of 42% of the 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 the PE patients) and in our study, the rate was detected as 45.3%. It was thought that these higher rates of incidental PE might be related with study population including different types of malignancies.

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 the history of chemotherapy on incidental PE were also evaluated in many studies (6, 19, 21). D'Izarn *et al* reported that advanced age was associated with unsuspected PE (22). In contrast to their study, patients with incidental PE were similar with symptomatic PE regarding age and gender distribution (21) in our study. 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 in the age and gender between the symptomatic and incidental cases.

Pulmonary embolism was more prevalent among patients with metastatic disease (7% *vs* 2%, $p < 0.007$) and in patients who had received recent chemotherapy (11% vs 3%, $p < 0.008$) (12). Also, it was suggested that recent chemotherapy was associated with unsuspected PE (UPE) (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 the presence of metastatic disease at the time of PE in Shinagare *et al* study (19). In our study, 66.3% of the patients had metastatic disease and 76.3% of them had history of chemotherapy at the time of their PE diagnosis. But, when the incidental cases were compared with the symptomatic ones, no statistically significant difference was found with respect to the history of chemotherapy

and the presence of metastasis. This might be explained by a significant portion of this study's sample who had histories of metastases and chemotherapy.

When evaluating the location of thrombus, it was found that 7.7% of the patients had thrombus in the main pulmonary artery, 14.6% of them had it in the right/left pulmonary arteries, 28.5% of them had it in the lobar arteries and 49.2% of them had it in the segmental/sub-segmental arteries (23). Another study from Turkey revealed that 2.4% of the patients had thrombus in the pulmonary truncus, 12.3% of them had it in the right/left pulmonary arteries, 57% of them had it in the lobar arteries and 28.3% of them had it in the segmental/sub-segmental arteries (24). A total of40% of the cases had involvement of main pulmonary artery and 50.6% of them had involvement of lobar arteries in our study. Shinagare *et al* suggested that suspected PE is more commonly involved with the main/lobar pulmonary arteries, while unsuspected PE is more frequently involved with the segmental arteries (19). The location of thrombus in the main pulmonary artery is increased in symptomatic cases compared with the incidental ones in our study; however, the difference was not statistically significant. They were both retrospective studies, but Shinagare *et al* study population included only patients with lung cancer, while our study sample covered all of the malignancies. This might be the explanation for the non-significant difference.

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

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

Recent data suggested that cancer patients with unsuspected PE had similar mortality rates as cancer patients with symptomatic PE (5, 22). When adjusted for tumour stage and performance status, 6-month mortality did not differ between the patients with UPE and patients without PE (22). So, the current guidelines recommend using the same approach to type and duration of anticoagulation, as it is used for patients with suspected PE. Among cancer patients, the bulk of available data suggests that incidental PE is associated with recurrent VTE and, when symptomatic, may adversely impact patients' survival (7). Our incidentally detected patients also had anticoagulant therapy as the symptomatic cases too.

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

CONCLUSION

A considerable number of PTE 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 RV functions could be the reason for the asymptomatic events.

REFERENCES

1. Abdel-Razeq HN, Mansour AH, Ismael YM. Incidental pulmonary embolism in cancer patients: clinical characteristics and outcome—a comprehensive cancer center experience. Vasc Health Risk Manag 2011; **7:** 153–8.
2. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007; **110:** 2339–46.
3. Dentali F, Ageno W, Becattini C, Galli L, Gianni M, Riva N et al. Prevalence and clinical history of incidental, asymptomatic pulmonary embolism: a meta-analysis. Thromb Res 2010; **125:** 518–22.
4. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer 2010; **102 Suppl 1:** S2–9.
5. den Exter PL, Jiménez D, Kroft LJM, Huisman MV. Outcome of incidentally diagnosed pulmonary embolism in patients with malignancy. Curr Opin Pulm Med 2012; **18:** 399–405.
6. Bach AG, Schmoll HJ, Beckel C, Behrmann C, Spielmann RP, Wienke A et al. Pulmonary embolism in oncologic patients: frequency and embolus burden of symptomatic and unsuspected events. Acta Radiol 2014; **55:** 45–53.

7. O'Connell C. How I treat incidental pulmonary embolism. Blood 2015; **125:** 1877–82.
8. O'Connell CL, Liebman HA. Approach to the management of incidental venous thromboembolic events in patients with cancer. J Natl Compr Canc Netw 2014; **12:** 1557–60.
9. Di Nisio M, Ferrante N, De Tursi M, Iacobelli S, Cuccurullo F, Büller HR et al. Incidental venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Thromb Haemost 2010; **104:** 1049–54.
10. Aleem A, Al Diab AR, Alsaleh K, Algahtani F, Alsaeed E, Iqbal Z et al. Frequency, clinical pattern and outcome of thrombosis in cancer patients in Saudi Arabia. Asian Pac J Cancer Prev 2012; **13:** 1311–5.
11. Reynolds MW, Shibata A, Zhao S, Jones N, Fahrbach K, Goodnough LT. Impact of clinical trial design and execution-related factors on incidence of thromboembolic events in cancer patients: a systematic review and meta-analysis. Curr Med Res Opin 2008; **24:** 497–505.
12. Browne AM, Cronin CG, English C, NiMhuircheartaigh J, Murphy JM, Bruzzi JF. Unsuspected pulmonary emboli in oncology patients undergoing routine computed tomography imaging. J Thorac Oncol 2010; **5:** 798–803.
13. van Es N, Bleker SM, Di Nisio M. Cancer-associated unsuspected pulmonary embolism. Thromb Res 2014; **133 Suppl 2:** S172–8.
14. Sack GH Jr, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. Medicine 1977; **56:** 1–37.
15. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine 1999; **78:** 285–91.
16. Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000; **343:** 1846–50.
17. Connolly GC, Menapace L, Safadjou S, Francis CW, Khorana AA. Prevalence and clinical significance of incidental and clinically suspected venous thromboembolism in lung cancer patients. Clin Lung Cancer 2013; **14:** 713–8.
18. Menapace LA, Peterson DR, Berry A, Sousou T, Khorana AA. Symptomatic and incidental thromboembolism are both associated with mortality in pancreatic cancer. Thromb Haemost 2011; **106:** 371–8.
19. Shinagare AB, Okajima Y, Oxnard GR, Dipiro PJ, Johnson BE, Hatabu H et al. Unsuspected pulmonary embolism in lung cancer patients: comparison of clinical characteristics and outcome with suspected pulmonary embolism. Lung Cancer 2012; **78:** 161–6.
20. Al Diab AI. Cancer-related venous thromboembolism: insight into underestimated risk factors. Hematol Oncol Stem Cell Ther 2010; **3:** 191–5.
21. Shteinberg M, Segal-Trabelsy M, Adir Y, Laor A, Vardi M, Bitterman H. Clinical characteristics and outcomes of patients with clinically unsuspected pulmonary embolism versus patients with clinically suspected pulmonary embolism. Respiration 2012; **84:** 492–500.
22. D'Izarn MS, Prim AC, Planquette B, Revel MP, Avillach P, Chatellier G et al. Risk factors and clinical outcome of unsuspected pulmonary embolism in cancer patients: a case-control study. J Thromb Haemost 2012; **10:** 2032–8.
23. de Monyé W, van Strijen MJ, Huisman MV, Kieft GJ, Pattynama PM. Suspected pulmonary embolism: prevalence and anatomic distribution in 487 consecutive patients. Advances in New Technologies Evaluating the Localization of Pulmonary Embolism (ANTELOPE) Group. Radiology 2000; **215:** 184–8.
24. Duru S, Ergün R, Dilli A, Kaplan T, Kaplan B, Ardıç S. Clinical, laboratory and computed tomography pulmonary angiography results in pulmonary embolism: retrospective evaluation of 205 patients. Anadolu Kardiyol Derg 2012; **12:** 142–9.
25. Şimşek A, Türkkan Ö, Melek K, Eyüboğlu FÖ. Assessment of patients with pulmonary thromboembolism (PTE) diagnosed in our clinic: 5 years experience. Turk Toraks Derg 2010; **11:** 149–54.
26. Remy-Jardin M, Pistolesi M, Goodman LR, Gefter WB, Gottschalk A, Mayo JR et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner society. Radiology 2007; **245:** 315–29.
27. In E, Turgut T, Kalkan M, Karadağ MO, Dağlı MN. The relationship between computed tomography pulmonary angiography findings and right ventricular dysfunction in patients with pulmonary embolism. Turk Toraks Derg 2014; **15:** 117–21.
28. Cok G, Tasbakan MS, Ceylan N, Bayraktaroglu S, Duman S. Can we use CT pulmonary angiography as an alternative to echocardiography in determining right ventricular dysfunction and its severity in patients with acute pulmonary thromboembolism? Jpn J Radiol 2013; **31:** 172–8.
29. Schoepf UJ, Kucher N, Kipfmueller F, Quiroz R, Costello P, Goldhaber SZ. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. Circulation 2004; **110:** 3276–80.
30. Nural MS, Elmali M, Findik S, Yapici O, Uzun O, Sunter AT et al. Computed tomographic pulmonary angiography in the assessment of severity of acute pulmonary embolism and right ventricular dysfunction. Acta Radiol 2009; **50:** 629–37.