http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i12.18

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Diagnostic Approach for Pulmonary Embolism on Solid Cancer Patients: A Case Series

Authors
Noviana Joenputri[1*], Eka Widya Khorinal[1]
[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Dharmais Cancer Hospital, Indonesia
*Corresponding Author
Noviana Joenputri, MD
Division of Hematology and Medical Oncology, Department of Internal Medicine, Dharmais Cancer Hospital, Indonesia
Letjen S.Parman St No.84-86, RT.4/RW.9
South Bambu City, Palmerah, West Jakarta City, Jakarta 11420

Abstract
Solid cancer patients have higher risk to get Venous Thromboembolism (VTE) compared to normal population, particularly on solid cancer patients with histopathology type of adenocarcinoma, advanced stage, cancer treatment, and immobilized. VTE can be in the form of Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE). PE incident in cancer patients resulted in high mortality between 30 to 80% and often not properly diagnosed because 81% of the cases did not show any symptoms.
This is a serial case from six cancer patients who were diagnosed with PE. According to the Revised Geneva Score, three patients were in the category of high risk, and three patients were in moderate risk of PE. All six patients had elevated D-dimer value, and therefore, according to the algorithm from the International SocietyonThrombosisand Hemostasis (ISTH) in 2017, the confirmation of PE diagnosis is to be done by performing gold standard imaging test, where perfusion lung scan is considered one of it. All six patients had the type of cancer histopathology of adenocarcinoma, with advanced stage, had various VTE risk factors, and showed symptoms, such as shortness of breath, pleuritic chest pain, swelling on extremity, and hemoptysis. Patients who were diagnosed with PE received anticoagulant treatment according to the standard therapy.
Vigilance must be exercised if PE is suspected, particularly in cancer patients with high or moderate Revised Geneva Score. It is expected that screening will lead to adequate management which then result on the reduction of mortality due to PE.
Keywords: *Venous thromboembolism, pulmonary embolism, solid cancer.*

Introduction

Venous thromboembolism (VTE) consists of two related conditions, i.e. deep vein thrombosis (DVT) and pulmonary embolism (PE). The underlying conditions which cause thrombosis include damaged vascular endothelial, static blood flow, and blood hypercoagulability. Many factors are known to increase VTE risk, such as old age, female gender, obesity, fracture (pelvis and lower extremities), major surgery, major trauma, spinal

cord injury, chemotherapy, congestive heart failure, respiratory failure, hormonal therapy, malignancy, pregnancy, previous VTE, thrombophilia, immobilization for more than three days, and varicose vein.[1]Several studies showed that cancer patients have four to seven times higher risk of VTE compared to the normal population.[2-5] 20-30% of all new VTE cases occur on cancer patients.[6] Factors which have strong relationship with VTE cases on cancer patients include the type and histopathology type of cancer, stage, therapy, and patient performance status.[7-11]Cancers with histopathology type of adenocarcinoma dan advanced stage or metastatic cancers have higher risk of VTE.[9,12,13] Therapy administered to cancer patients, such as chemotherapy, hormonal therapy, radiation therapy, and surgery, also increases VTE incidents on cancer patients compared to normal patients.[4,12,13]

PE is the most feared part of VTE because it has a high risk of mortality (30-80%), particularly if diagnosed late.[14-16] PE incidents increase three-folds in solid cancer patients with histopathology type of adenocarcinoma compared to the non-adenocarcinoma.[12,13] PE often occurs without showing any significant preliminary symptoms, hence it is often undiagnosed despite of high mortality.[17] Therefore, these serial cases are aimed to describe the diagnostic approach for solid cancer patients who are suspected to have pulmonary embolism.

Case Presentation

We are reporting six patients who were diagnosed with solid cancer. From six patients, the youngest is 43 years old (age range is from 43 to 63 years old), and all of themare females. From six patients, four were diagnosed with breast cancer and two were diagnosed with lung cancer, and all are advanced stage cancers. Several symptoms were shown on these patients, but mostly are atypical symptoms, such as shortness of breath and coughing. Other symptoms which arose were pleuritic chest pain (2 out of 6 patients), hemoptysis (2 out of 6 patients), and unilateral extremities pain (1 out of 6 patients). Four out of six patients experienced unilateral swelling of lower extremities in the past one month. All patients had immobilization for more than three days due to hospitalization in the inpatient ward.Several patients were undergoing cancer treatment, such as chemotherapy (2 out of 6 patients), hormonal therapy (1 out of 6 patients), radiation therapy (2 out of 6 patients), or blood transfusion (3 out of 6 patients). On vital signs measurement, all patients had history of rapid heart rate and respiratory rate, as well as various performance status. Demographic data, medical history, and physical examination of the patients are shown in Table 1.

Wells score assessment was performed on the six patients, five patients were found to have high risk of DVT and 1 patient hasmoderate risk of DVT. Confirmation of DVT was then obtained through Doppler ultrasound assessment on bilateral lower extremities, and the six patients were confirmed to have DVT on lower extremities. After that, Revised Geneva score assessment was performed, and it was found out that three patients have moderate risk of PE and three patients have high risk of PE (Table 2).

According to laboratory results, all six patients had elevatedD-dimerlevel with 36,300 ng/mL as the highest value (the range is from 1,870 ng/mL to 36,300 ng/mL). All patients underwent perfusion lung scan and defects on segments in the lung were found on all six patients (Figure 1).

Table 1. Demographic data, risk factors, performance status, and vital signs

Pt No	Age/ Sex	Solid Cancer	Complaints	Risk Factors	Performance Status and Vital Signs
1	63/F	Breast adenocarcinoma, Stage 4	Shortness of breath (-), pain on right extremities	Immobilization (+), chemotherapy (+), history of VTE (+) 3 years ago, swelling of right lower limb (+)	ECOG : 1; BP : 130/80 mmHg HR : 98x/min; RR : 22x/min
2	62/F	Breast adenocarcinoma, Stage 4	Shortness of breath (+), cough (+)	Immobilization (+), radiation therapy (+), hormonal therapy (+), swelling of left lower limb (+)	ECOG : 4; BP : 140/80 mmHg HR : 104x/min; RR : 23x/min
3	43/F	Breast adenocarcinoma, Stage 4	Shortness of breath (+)	Immobilization (+), blood transfusion (+)	ECOG : 3; BP : 140/100 mmHg HR : 123x/min; RR : 26x/min
4	49/F	Lung adenocarcinoma, Stage 4	Shortness of breath (+), cough (+)	Immobilization (+), radiation therapy (+), swelling of left lower limb (+)	ECOG : 2; BP : 120/80 mmHg HR : 96x/min; RR : 20x/min
5	54/F	Lung adenocarcinoma, Stage 3	Shortness of breath (+), pleuritic chest pain (+), cough (+), hemoptysis (+)	Immobilization (+), chemotherapy (+), blood transfusion (+)	ECOG : 2; BP : 110/70 mmHg HR : 120x/min; RR : 26x/min
6	50/F	Breast adenocarcinoma,Stage 4	Shortness of breath (+), pleuritic chest pain (+), cough (+), hemoptysis (+)	Immobilization (+), blood transfusion (+), swelling of right lower limb (+)	ECOG : 2; BP : 110/70 mmHg HR : 100x/min; RR : 22x/min

Table 2. Data of DVT and PE assessments of the patients

Pt.No	Age/Sex	Wells Score	DVT (Doppler Ultrasound)	Revised Geneva Score	D-dimer	Perfusion Lung Scan
1	63/F	5 (high risk of DVT)	Positive	17 (high risk of PE)	4,030	**Pulmonary embolism (+)** Subsegmental perfusion defects in the right lung
2	62/F	4 (high risk of DVT)	Positive	10 (moderate risk of PE)	4,630	**Pulmonary embolism (+)** Subsegmental perfusion defects in the right lung
3	43/F	2 (moderate risk of DVT)	Positive	10 (moderate risk of PE)	36,300	**Pulmonary embolism (+)** Small-moderate segmental perfusion defects in the superior lobe
4	49/F	3 (high risk of DVT)	Positive	10 (moderate risk of PE)	3,530	**Pulmonary embolism (+)** Segmental perfusion defects in several segments in the right lung
5	54/F	3 (high risk of DVT)	Positive	12 (high risk of PE)	14,190	**Pulmonary embolism (+)** Segmental and subsegmental perfusion defects in the right lung
6	50/F	3 (high risk of DVT)	Positive	12 (high risk of PE)	1,870	**Pulmonary embolism (+)** Subsegmental perfusion defects in the left lung

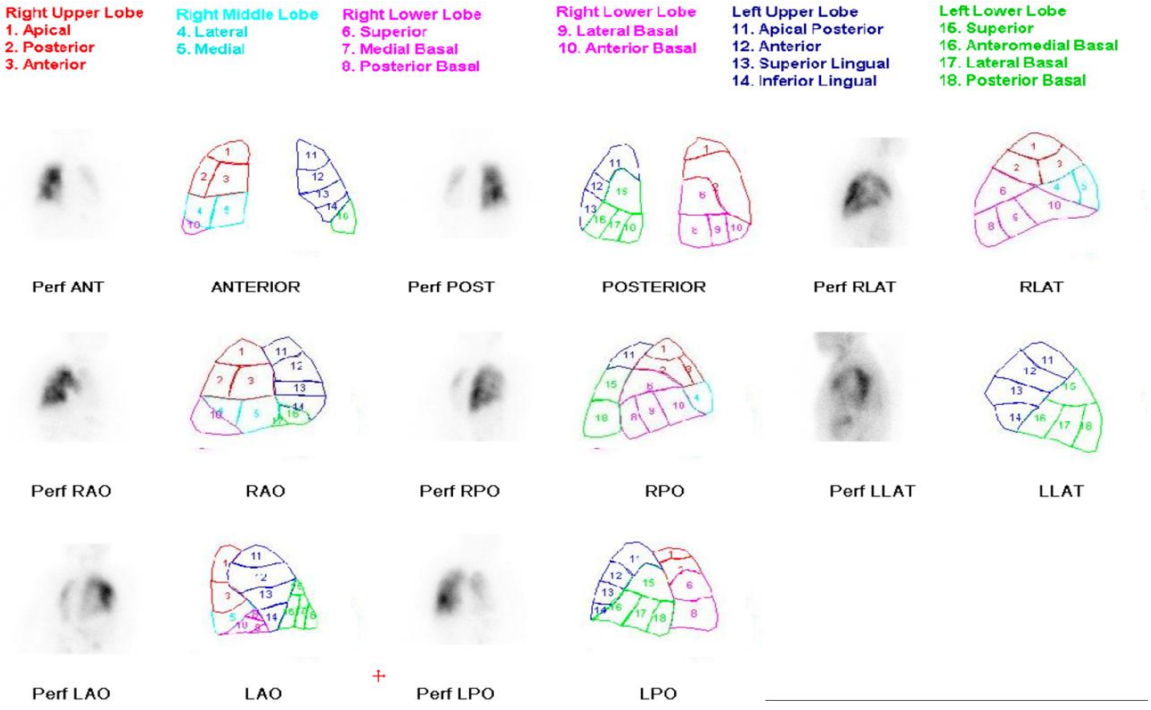

Figure 1. Result of perfusion lung scan of a patient

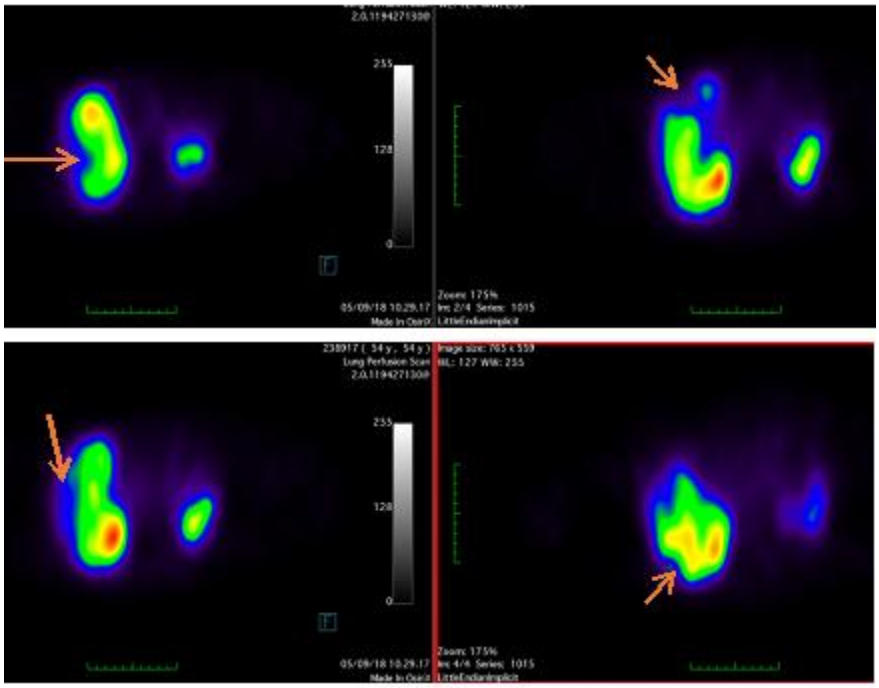

Figure 2 Result of perfusion single photon emission CT (P_{SPECT}). The arrows show the defects on the lung.

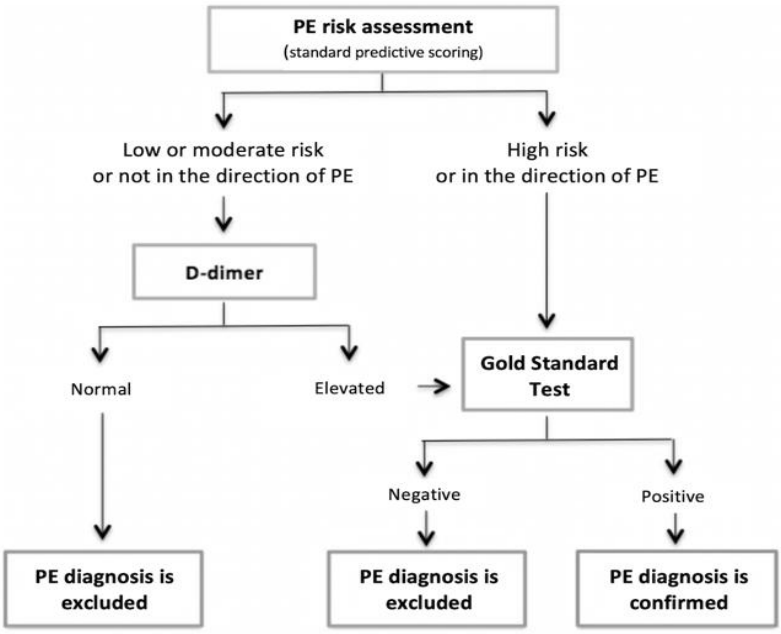

Figure 3. Algorithm for PE diagnosis according to the International Society on Thrombosis and Hemostasis (ISTH) in 2017

Discussion

Cancer patients have seven times higher risk of VTE than non-cancer population and this results in poor prognosis.[12] Cancer patients with thrombosis have four to eight times higher risk of mortality, and the survival rate of cancer patients with thrombosis compared to those without thrombosis is 12% and 36%, respectively ($p<0.001$).[4,10,18]

It had been reported that VTE risk factors which are related to patients include old age, female gender, low performance status, immobilization, and obesity.[2-6,18-21] According to demographic data of the patients in these serial cases, all six patients had risk factors which are known to increase VTE incidence, such as female gender, old age, and immobilized for more than three days.

A retrospective study showed that the type of cancer which is strongly related to thrombosis is cancer with histopathology type of adenocarcinoma which produces mucin, such as pancreatic cancer, lung cancer, stomach cancer, and adenocarcinoma with unknown primary cancer.[5,11,12] Another study reported that thrombosis is found more frequent on patients with advanced stage cancer who received anti-cancer treatment.[9] The administration of systemic chemotherapy and major surgery also increase the incidence of thrombosis.[2,4,6]In these serial cases, all six solid cancer patients had histopathology type of adenocarcinoma, where some of them had lung cancer and the remainings had breast cancer.Most of the patients were also in advanced stage and received various cancer treatment.

In cancer patients, hypercoagulation can be caused by activation of coagulation cascade and platelets, increase of endothelial adhesion, suppression of fibrinolysis, inhibition of Cprotein pathway, and other risk factors, such as the use of cytostatic and hormonal medication.[4] Cytostatic medication can affect the level of coagulation protease enzymesand can directly damage the endothelium which then lead to the release of tissue factors. Hormonal medication decreases the level of natural anticoagulant. Venous stasis due to bed rest or extrinsic vascular compression by the tumor mass can cause thrombosis on cancer patients.[10,22]All six patients had high plasma D-dimer level. Plasma D-dimer level in cancer patients were elevated as result of the cancer itself or the administered treatment, such as surgery and chemotherapy.

Two meta-analysis studies confirmed the validity of original and simplified versions of Wells Score and Revised Geneva Score as predictive value for PE.[23,24,25]Five out of six patients had Wells Score indicative of high risk of DVT and they were confirmed by Doppler ultrasound assessment to have DVT on lower extremities. Wells scoring system consists of several signs and symptoms, as well as risk factors, which then categorized patients into low, moderate, and high risk.[26]

Revised Geneva Score has 9 parameters with positive predictive value of 81% and negative predictive value of 63%.[27] Revised Geneva Score categorizes patients into three PE risk categories. According to the calculation of Revised Geneva Score, three patients were in the category of high risk of PE and three other patients were in the category of moderate risk of PE. PE diagnosis can be confirmed according to the algorithm published by the International Society on Thrombosis and Hemostasis (ISTH) in 2017 (Figure 3).[18] According to the respective algorithm, patients who have low and moderate risks or not in the direction of PE should have their plasma D-dimer level assessed. If the plasma D-dimer level is normal, then PE diagnosis can be excluded. However, if there is an increase in plasma D-dimer level, gold standard test, such as lung CT scan or lung perfusion scan, must be performed. If the result of gold standard test is negative, then PE diagnosis can be excluded. If a patient falls into the category of high risk of PE, then gold standard test must be immediately performed without assessing the D-dimer level.If the test shows positive result, then PE diagnosis can be confirmed.[18]Perfusion lung scan or perfusion single photon emission CT (P_{SPECT}) is accurate in diagnosing or excluding PE with 90% sensitivity and 95% specificity. Positive and negative predictive value for $P_{SPECT}$is 91% (95% CI 80-97%) and 94% (95% CI 86-97%), respectively, in diagnosing pulmonary embolism.[29]

In these serial cases, three patients had moderate risk of PE with elevated plasma level of D-dimer. The result of perfusion lung scan also showed perfusion defects in several lung segments. Therefore, these three patients were diagnosed with pulmonary embolism.The other three patients had high risk of PE. In accordance with the ISTH 2017 algorithm, gold standard test was immediately performed on these three patients without assessing the plasma level of D-dimer. Results of perfusion lung scan showed defects in lung segments of these three patients, and therefore they were diagnosed with pulmonary

embolism. All patients who were diagnosed with pulmonary embolism received anticoagulant treatment according to the standard therapy.

Conclusion

Vigilance must be exercised if PE is suspected, particularly on cancer patients with high or moderateRevised Geneva Score for PE. It is expected that screening will lead toadequate management which then result on the reduction of mortality due to PE.

References

1. Anderson Jr FA, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23_suppl_1):I-9.
2. Khalil J, Bensaid B, Elkacemi H, Afif M, Bensaid Y, Kebdani T. Venous thromboembolism in cancer patients : an underestimated major health problem. World J Surg Oncol. 2015;13: p1–17.
3. Falanga A, Zacharski L. Deep vein thrombosis in cancer: The scale of the problem and approaches to management. Ann Oncol. 2005;16: p696–701.
4. Heit JA. Cancer and venous thromboembolism : Scope of the Problem. Cancer Control 2005; p12:5–10.
5. Khorana AA. Cancer-associated thrombosis: updates and controversies. American Society of Hematology. 2015: p626–30.
6. Ay C, Marosi C, Chiriac A-L, Vormittag R, Simanek R, Quehenberger P, et al. Prediction of venous thromboembolism in cancer patients. Blood. 2010;116: p5377–82.
7. Streiff MB. Association between cancer types, cancer treatments, and venous thromboembolism in medical oncology atients. Clinical Advances in Hematology & Oncology. 2013;11(6): p349–57.
8. Ashrani AA, Gullerud RE, Petterson TM, Marks RS, Bailey KR, Heit JA. Risk factors for incident venous thromboembolis in active cancer patients: A population based case-control study. Thromb Res. 2016;139: p29–37.
9. Gade IL, Braekan SK, Naes IA, Hansen JB, Cannegieter SC, Overvad K, et all. The impact of initial cancer stage on the incidence of venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) Cohort. J of Thromb and Haemost. 2017;15(8): p1567–75.
10. Buller HR, Van Doormaal FF. Sluis V, Kamphuisen PW. Cancer and thrombosis: from molecular mechanisms to clinical presentations. J of Thromb and Haemost. 2007;5: p246–54.
11. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010;102: S2–9.
12. Blom JW, Osanto S, Rosendaal FR. The risk of a venous thrombotic event in lung cancer patients : higher risk for adenocarcinoma than squamous cell carcinoma. J of Thromb and Haemost. 2004;2: p1760–5.
13. Vitale C, D'Amato M, Calabrò P, Stanziola AA, Mormile M, Molino A. Venous thromboembolism and lung cancer: a review. Multidiscip Respir Med. 2015;10(28): p1–9.
14. Sweet PH, Theodore III, John A, Masliah E, Witucki P. Fatal pulmonary embolism update : 10 years of autopsy experience at an academic medical center. J R Soc Med Sh Rep. 2013;4: p1–5.
15. O'Connell CL, Boswell WD, Duddalwar V, Caton A, Mark LS, Vigen C, Liebman HA. Unsuspected pulmonary emboli in cancer patients: clinical correlates and relevance. Journal of Clinical Oncology. 2006 Oct 20;24(30):4928-32.
16. Task Force Members: Konstantinides S V, Germany C, France ND, Uk DF, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. European Heart Journal.

2014;10: p1-48.
17. Gary T, Belaj K, Hafner F, Froehlich H, Samonigg H, Pilger E, et all. Asymptomatic deep vein thrombosis and superficial vein thrombosis in ambulatory cancer patients : impact on short-term survival. B J Cancer 2012;107: p1244–8.
18. Mozaheb Z. Cancer and thrombosis. J Hematol Thrombo Dis. 2014;2(6):p8–11
19. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2017;122(10): p1712–24.
20. Streiff MB. Association between cancer types, cancer treatments, and venous thromboembolism in medical oncology atients. Clinical Advances in Hematology & Oncology. 2013;11(6): p349–57.
21. Ashrani AA, Gullerud RE, Petterson TM, Marks RS, Bailey KR, Heit JA. Risk factors for incident venous thromboembolis in active cancer patients: A population based case-control study. Thromb Res. 2016;139: p29–37.
22. Levitan N, Dowlati A, Remick SC, et all. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy: risk analysis using Medicare claim data. Medicine. 1999;78: 285-91.
23. Ceriani E, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Throm b Haemost 2010; 8: 957–70.
24. Lucassen W, etal. Clinical decisionrules for excluding pulmonary embolism: a meta-analysis. Ann Intern Med 2011; 155: 448–60.
25. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, Perrier A. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Annals of internal medicine. 2006 Feb 7;144(3):165-71.
26. Kyrle PA, Eichinger S. Deep vein thrombosis. Lancet. 2005;365: p1163–74.
27. Klok FA, Kruisman E, Spaan J, Nijkeuter M, Righini M, Aujesky D. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. J Thromb and Haemost. 2008;6: p40–4.
28. Righini M, Ebadi HR, Gal GL. Diagnosis of acute pulmonary embolism. J Thromb and Haemost. 2017;15: p1251–61
29. Bajc M, Miniati M, Jögi J, Stein PD. Perfusion SPECT in patients with suspected pulmonary embolism. European journal of nuclear medicine and molecular imaging. 2013 Sep 1;40(9):1432-7.