Approaches of Physicians for the Diagnosis and Treatment of Pulmonary Thromboembolism: A Questionnaire Study

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Abstract

Objective: We aimed to demonstrate the approaches of physicians with a questionnaire toward the patients with pulmonary thromboembolism (PTE) in our country.

Methods: An invitation letter including a questionnaire with 28 questions to assess the approaches they prefer in the patients with PTE and the capabilities of the departments they work at and a link for the questionnaire was directed to the mail groups of chest diseases specialists. Responses of the physicians who participated in the questionnaire were reviewed.

Results: The examinations used to diagnose PTE such as D-dimer, troponin, echocardiographic Doppler ultrasonography and multidetector computed tomography (CT) have been performed in 94% of the institutions, ventilation/perfusion scintigraphy, MRI and pulmonary angiography examinations were performed in 50% of the instututions. While D-dimer test was performed in 73.2% of the institutions by quantitative ELISA; in 15.7% of them it was semiquantitative and in 11.6% of the instutitions it was performed by latex agglutination. 81% of physicians were seen to be using clinical probability scoring systems and most commonly used scoring method was seen to be Wells scoring with a rate of 90%. According to the simplified PESI score, 61.5% of the physicians reported to prefer outpatient treatment. In non-massive and submassive pulmonary thromboemboli patients, 86.2% of the physicians reported to prefer thr low molecular weight heparin (LMWH) treatment; vitamin K antagonist in maintenance treatment was also the most commonly resorted drug with a percentage of 84.9.

Conclusion: The absence of the examinations used in the diagnosis and treatment of PTE in most institutions and difficulty to reach the available examinations at all hours of the day were significant facts. Especially; lack of access to high-sensitivity D-dimer test, bedside echocardiography used to assess right ventricular dysfunction, troponin and NT-proBNP makes us think about low adaptation to guidelines.

Keywords: Pulmonary embolism, diagnosis, treatment, D-dimer

INTRODUCTION

Pulmonary thromboembolism (PTE) is still one of the main causes of death in hospitals despite new developments in its diagnosis and treatment. Clinical suspicion is the most important step in reaching a diagnosis of PTE. PTE must be particularly suspected in patients with dyspnea and tachycardia, in cases of normal chest radiography, and in the absence of any other disease that can explain the condition of the patient. While it can occur without any clinical symptoms, it can result in mortality with an acute and chronic course. Its incidence was reported to be 100–200 per 100000 people in the 2000s (1, 2). The European Society of Cardiology published the first guidelines for the diagnosis and treatment of acute PTE in 2008 (3). These guidelines were updated in 2014 in light of the results from new studies (4). The most significant changes in the updated guidelines are related to a clearer risk classification, patient management according to risk category, and improvements in the treatment. In Turkey, a consensus report was first published by the Turkish Thoracic Society (TTS) in 2009 in order to establish a standard approach for the diagnosis and treatment of this important disease and to reduce the differences among clinics and physicians (5). This report was updated in 2015 (6). Thus, it was aimed to decrease the mortality, morbidity, and unnecessary health-care costs associated with this disease.

Despite the guidelines that have been designed, different approaches are seen in the diagnosis and treatment of PTE patients in association with the opportunities that institutions have in Turkey. In this study, we aimed to present physicians' approaches forthe diagnosis and treatment of PTE cases in Turkey and to investigatethe presence of PTE evaluation opportunities that could provide a suitable approach for this disease at their institutions by using a questionnaire.

METHODS

A link to the web-based questionnaire, consisting of 28 items, was sent to the e-mail addresses of chest diseases specialists to ensure that each participant would only answer the questionnaire once. Moreover, societies could participate in this questionnaire study through e-mail groups. Approval was received for this study from the Ethics Committee of İzmir Dr. Suat Seren Education and Research Hospital for Thoracic Diseases and Surgery.

The physicians were asked to answer the questionnaire considering their own attitudes and behaviors. The questionnaire included questions in different categories about the availability of D-dimer test, cardiac markers (troponin, pro-BNP, and others), and imaging techniques (multi-slice computed tomography, V/P scintigraphy, Doppler ultrasonography, and others), treatment, and follow-up, in addition to the duration for which the physician had worked as a specialist and the features of the hospital where they worked (university, education hospital, public hospital, and others).

While the participants were asked to make one choice in some questions, they were allowed to choose more than one answer in some other questions. The questions included in the questionnaire are given in Table 1.

Statistical Analysis

While evaluating the answers given in the questionnaire, actual numbers and percentages (%) from the descriptive statistics were used. In cases with more than one answer, the number of responses and percentage were used. The percentage values were presented in bar graphs and pie charts. Crosstabs were employed for showing the distribution of examination techniques used in the hospitals where the physicians worked. The data obtained from the study were entered into a database designed through Statistical Package for the Social Sciences for Windows version 16.0 software (SPSS Inc. Released 2007, Chicago, IL, USA), and statistical analyses of the data were performed using the same statistic program.

RESULTS

A total of 159 chest diseases specialists answered the questionnaire. Of the participants, 39.2% were working in universities, 25.3% were working in public hospitals, 14.5% were working in education and research hospitals for chest diseases, 10.1% were working in private hospitals, and 8.8% were working in research hospitals for general education. Of the physicians, 46.5% were specialists, 38.6% were lecturers, and 15% were research assistants. Emergency services were provided in 98.1% of the hospitals that they worked at.

Of the examination techniques used for the diagnosis of pulmonary thromboembolism, while D-dimer and troponin levels, echocardiographic examination, Doppler USG, and multi-slice computed tomography (CT) were used in 92.4%, 94.9%, 94.9%, 90.5%, and 92.4% of participants' hospitals, respectively, ventilation/perfusion scintig-

raphy, MR imaging, and pulmonary angiography were performed in 55.9%, 53.4%, and 47.8%, respectively (Figure 1). While D-dimer test was performed through quantitative ELISA in 73.2% of hospitals, it was performed through a semi-quantitative method in 15.7% of hospitals, and via latex agglutination in 11.6% (Figure 2).

Of the examinations used for the diagnosis of pulmonary thromboembolism, D-dimer and troponin levels were used in 90% of the institutions while multi-slice CT was used in 75% of the institutions almost every time. However, NT-pro-BNP, echocardiography, and V/P scintigraphy were performed at lower rates (Table 2). While both Doppler USG and echocardiography, which could be used at the patient's bedside, were performed in 27.5% of the institutions, 34.5% used only echocardiography, while 34.5% used only Doppler USG, and 3.1% used none of them (Figure 3).

In total, 81% of the physicians used clinical probability scoring systems, with the most common scoring technique being Wells scoring, at a rate of 90% (Figure 4). After the establishment of the diagnosis of PTE, 66.4% of the physicians stated that they undertook the diagnosis and treatment of all embolism cases, while 17.7% said that they referred only massive and submassive embolism cases and 12.6% mentioned that they decided on the referral of each patient according to the follow-up period (Table 3). According to the simplified PESI score, 61.5% of physicians preferred outpatient treatment (Figure 5).

While 86.2% of the physicians preferred low-molecule weighted heparin treatment (LMWH) in non-massive and submassive PTE patients, the most used drug in the maintenance treatment was vitamin K antagonist, at a rate of 84.9% (Figures 6, 7). After the completion of PTE treatment, 56.8% of physicians always requested an imaging technique and 32.5% sometimes requested one for evaluating the condition of embolism. The most commonly requested imaging techniques were multi-slice CT (77.6%), echocardiography (48%), and Doppler USG (57.8%), respectively (Figure 8). While 81.2 % of the physicians stated that they directed patients diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) for endarterectomy, it was not performed in 89.2% of their institutions.

DISCUSSION

The approaches for the diagnosis and treatment of pulmonary thromboembolism are improving in line with new studies. It is important that a physician must have adequate opportunities to evaluate a patient suspected to have PTE. In this questionnaire study, we aimed to present a picture of physicians' approaches for the diagnosis and treatment of PTE patients in Turkey in order to reveal their general tendencies and to show the opportunities in the hospitals where these physicians worked. According to the data obtained from the questionnaire results, it was found that the institutions where the participants worked did not have sufficient opportunities for some examinations in the diagnosis of PTE patients.

As is known, the most important step in the diagnosis of PTE is a suspicion of the disease. Moreover, an accompanying risk factor must be questioned and other diagnoses must be ruled out. The absence of clinical and physical examination findings specific to PTE makes the establishment of diagnosis more difficult. Although chest radiography, electrocardiography (ECG), biochemical analyses, and arterial blood gases contribute to the clinical evaluation, these examinations are particularly useful for ruling out other causes. In addition to these

Anar et al. Approaches of Physicians for Pulmonary Thromboembolism

Eurasian J Pulmonol 2016; 18: 96-103

Table 1. Questions included in the questionnaire

Question 1: What is your age (Year of birth)?

Question 2: What is your position at the institution?

Question 3: How long have you been working in the area of chest diseases?

Question 5: What is the name of your institution?

Question 6: Does your hospital provide emergency service?

Question 7: How many patients with pulmonary embolism have you examined in the last one year?

* Question 8: Which of following examination techniques can be performed for the diagnosis of PTE atyour institution?

D-dimer level, troponin level, NT-pro-BNP, echocardiographic examination, Doppler USG, multi-slice CT, V/P scintigraphy, MR imaging, pulmonary angiography, vena cava inferior filter

Question 9: Which of following examination techniques can be performed at bedside for the diagnosis of PTE atyour institution?

Echocardiography, Doppler USG, none, all

Question 10: If the D-dimer test performed atyour institution, which method is used?

quantitative, semi-quantitative, qualitative

* Question 11: Which of following examinations can always be performed and evaluated in your institution?

D-dimer test, troponin test, NT-pro-BNP examination, echocardiographic examination, Doppler USG, multi-slice CT, V/P scintigraphy, MR imaging, pulmonary angiography

Question 12: Do you evaluate the patients having PTE but not risk factor in terms of thrombophilia?

Question 13: Do you use PTE clinical probability scoring systems?

Question 14: If you use PTE clinical probability scoring systems, which one do you prefer mostly?

Wells, Geneve, Miniati, Charlotte, Hyers score, BTS scoring system, exclusion criteria for pulmonary embolism

Question 15: What do you do for a patient when you suspect PTE or diagnose PTE?

I immediately refer all patients; I refer only when I suspect massive or submassive embolism; I undertake the diagnosis and treatment of all embolism patients; I decide considering the follow-up independently of the patient's condition.

Question 16: Do you prefer outpatient treatment in proper cases according to sPESI score (sPESI<1)?

Question 17: Have you previously applied thrombolytic treatment in a patient diagnosed with PTE?

Question 18: Which drug do you often prefer as the initial treatment in clinically stable PTE patients without shock/hypotension (non-massive and/or submassive) (unfractionated heparin, LMWH, new oral anticoagulant, thrombolytic therapy)

Question 19: How long is the treatment in patients initiallydiagnosed with PTE (not associated with cancer and thrombophilia)?

 3–6 months, 6–12 months, >12 months

Question 20: Which of following drugs do you generally prefer for maintenance treatment?

UFH, LMWH, Vit K antagonist, Rivaroxaban, Dabigatran, Apixaban

Question 21: Do you request an imaging technique (DopplerUSG or angio-CT or V/P scintigraphy) for evaluating embolism while ending the treatment of PTE?

* Question 22: If you request an imaging technique, which one do you prefer?

I do not request an imaging technique, multi-slice CT, V/P scintigraphy, echocardiography, Doppler USG

Question 23: Do you perform D-dimer test one month after having stopped the treatment?

Question 24: How long do you follow up a patient whose treatment is discontinued?

I do not follow up, 3 months, 6 months, 12 months

Question 25: Do you direct CTEPH patients for endarterectomy?

Question 26: Is endarterectomy performed atyour institution?

Question 27: Is endarterectomy performed atyour institution?

Question 28: Is an inferior vena cava filter inserted atyour institution?

*Participants could mark more than one choice for these questions. CT: Computed tomography; LMWH: low-molecular weight heparin; MR: magnetic resonance; PTE: pulmonary thromboembolism; USG: ultrasonography; UFH: unfractionated Heparin; V/P: ventilation/perfusion
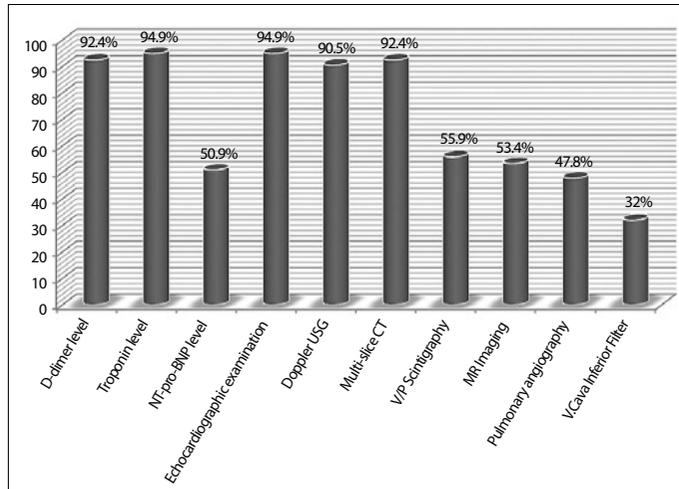
Figure 1. The distribution of examination techniques for the diagnosis of PTE at the institutions where participants worked
CT: Computed tomography; MR: magnetic resonance; NT-pro-BNP: N-Terminal B- type natriuretic peptide; USG: ultrasonography; V/P: ventilation/perfusion
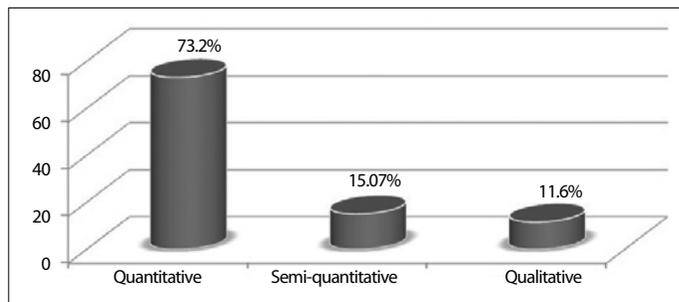

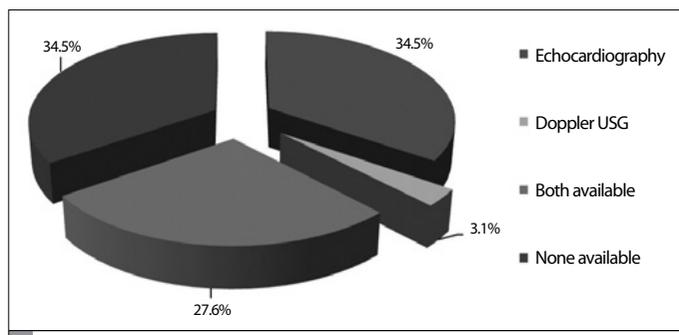**Figure 2.** The distribution of ways for performing the D-dimer test

Figure 3. The distribution of bedside examinations
USG: Ultrasonography

Figure 4. The distribution of clinical scoring systems used by physicians in PTE

Figure 5. The distribution of physicians preferring outpatient treatment in appropriate patients according to sPESI score (sPESI<1)
sPESI: Simplified Pulmonary Embolism Severity Index

Table 2. The examination techniques that can always be performed atthe institutions of the participants

Examination Techniques	n	%
D-Dimer level	144	91.40
Troponin level	142	89.87
NT-pro-BNP level	69	43.67
Echocardiographic examination	87	55.06
Doppler USG	48	30.38
Multi-slice computed tomography	119	75.32
Ventilation/perfusionscintigraphy	12	7.59
MR imaging	33	20.89
Pulmonary angiography	34	21.52

MR: Magnetic resonance; NT-pro-BNP: N-Terminal B-type natriuretic peptide; USG: ultrasonography

examination techniques, other techniques that are necessary for the establishment of diagnosis are D-dimer and troponin levels, echocardiographic evaluation, Doppler USG, multi-slice CT, NT-pro-BNP, ventilation/perfusion scintigraphy, MR imaging, and pulmonary angiography. Not only examinations but also good recognition of at-risk patient groups and the evaluation of clinical probability scorings are important for diagnosis. However, the scoring systems that were recommended previously did not seem easy for clinical practices. In the new guidelines, easier application ways are recommended for these scoring systems (Wells rule and revised Geneva score) (7, 8). In our study, 81% of physicians used clinical probability scoring sys-
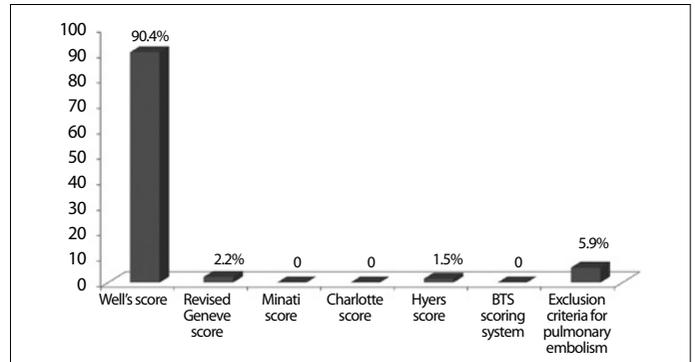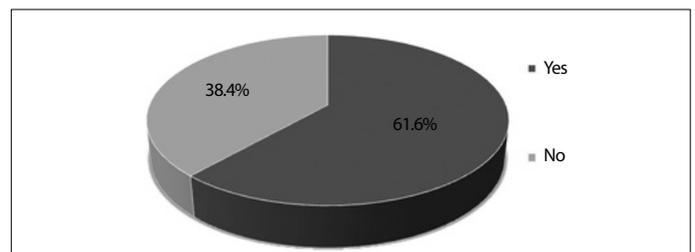
tems,with the most common scoring method being the Wells score, with a percentage of 90%, as stated in the guidelines. Accordingly, patients are put into three (PTE with low, moderate, and high probability) or two (probability of PTE and no probability of PTE) categories. The prevalence of venous thromboembolism (VTE) is low in patients with low and moderate clinical probability. If a negative result is obtained when D-dimer level is evaluated through a classical ELISA test with high sensitivity in these patients, additional imaging techniques for ruling out the disease are not needed (9, 10). When clinical probability and D-dimer level are evaluated together, the need for further procedures for diagnosis decreases at the rate of 30% (3).

Anar et al. Approaches of Physicians for Pulmonary Thromboembolism

Eurasian J Pulmonol 2016; 18: 96-103

Table 3. The attitudes of the physicians when they suspect pulmonary thromboembolism or when they establish the diagnosis of pulmonary thromboembolism

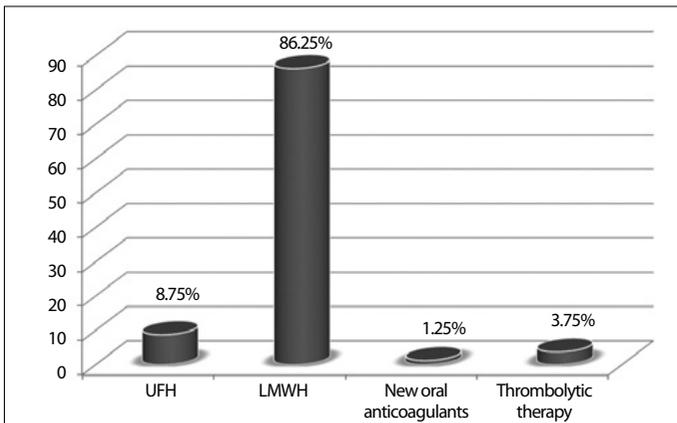|	n	%
I refer all patients with the suspicion of PTE.	5	3.16
I refer only when I suspect massive or submassive embolism.	28	17.72
I undertake the diagnosis and treatment of all embolism cases.	105	66.46
Independently of the patient's state, I decide considering the follow-up period in the hospital.	20	12.66

PTE: Pulmonary thromboembolism

Figure 6. The distribution of drugs often preferred by physicians as the initial treatment in clinically stable PTE patients without shock/hypotension (non-massive and/or submassive)
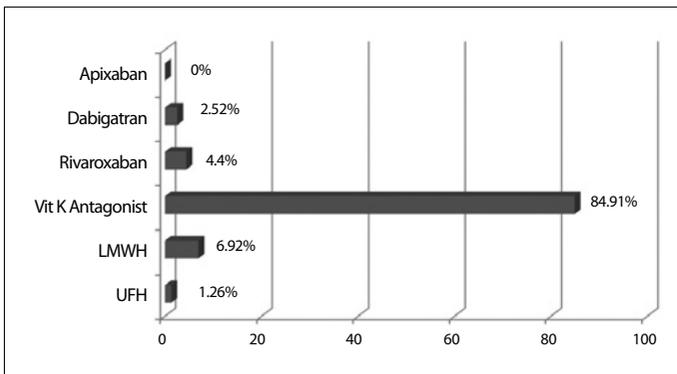LMWH: Low-molecular weight heparin; UFH: unfractionated heparin

Figure 7. The distribution of drugs preferred in the maintenance treatment of PTE
LMWH: Low-molecular weight heparin; UFH: unfractionated heparin

This method for exclusion is safely used in young patients without a comorbid disease and is also used in old patients and in patients having chronic obstructive pulmonary disease and heart failure and suspected to have PTE, except for those who have had surgery recently (11). In our study, it was found that the D-dimer level measurement was performed in 92.4% of the institutions, while quantitative ELISA was done in 73.2%. A semi-quantitative method was used in 15.7% of the institutions, while latex agglutination was performed in 11.6%.
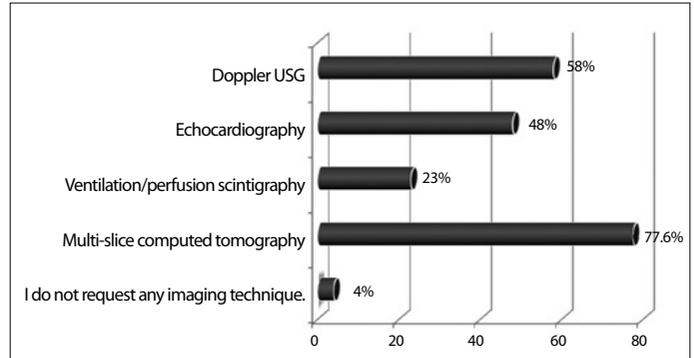

Figure 8. The distribution of examinations requested by physicians for evaluating the condition of embolism after the completion of PTE treatment
USG: Ultrasonography

Among these tests, while the least sensitive ones were classical latex agglutination and red cell agglutination tests (SimpliRED), the most sensitive ones were the ELISA and turbidimetric tests (12).Furthermore, the acceptance of age-adjusted cutoff values is recommended for D-dimer levels instead of stable cutoff values (above 50 years; age ×10 μg/L) because it is reported that D-dimer levels increase in parallel with age (13).

Advanced imaging techniques are used for proving thrombus when D-dimer test is positive. In patients whose chest radiography results are normal, the diagnostic value of perfusion scintigraphy is high alone, rather than with CT angiography (14). In our study, V/P scintigraphy was used only in 7.5% of the institutions almost every time. In the studies in which PTE was ruled out through normal scintigraphy, the 3-month VTE (venous thromboembolism) risk was found to be below 1% (15, 16). On the other hand, the result of scintigraphy was found to be normal in less than 20% of the patients suspected to have PTE (17). A high-probability V/P scintigraphy result helps diagnosis in patients with high and moderate clinical probability. In emergency units, diagnosis is established in patients suspected of PTE through V/P scintigraphy at the rate of 30–50% (18, 19). Because it has a lower radiation risk than CT, it can be preferred in young women, pregnant women, and patients with contrast agent allergy and with kidney failure (20).

If the possibility of PTE is high in clinical evaluation, the D-dimer level measurement is not used due to false positive results. It is emphasized that some imaging techniques, such as direct pulmonary CT angiography and V/P scintigraphy, must be used in such situations (4-6). It was found in our study that while multi-slice CT could be performed in 75% of the institutions almost every time, echocardiography and V/P scintigraphy were performed at lower rates. Echocardiography or cardiac markers (troponin, NT-pro-BNP) are important examination techniques that are used not only for the establishment of diagnosis but also for the evaluation of prognosis and pre-treatment risk.In various meta-analyses, a complicated clinical course and mortality rates were found to be significantly higher in patients with high troponin levels compared to those in patients with normal troponin levels (21, 22). BNP and pro-BNP are associated with hemodynamic disorder and right ventricular dysfunction in acute PTE (23). On the other hand, low levels of these tests in acute PTE were found to havea high negative predictive value for an early poor prognosis

(24, 25). Of the cardiac markers, troponin and NT-pro-BNP were evaluated in 90% and 43.6% of the institutions, respectively, almost every time, while, for the imaging techniques, multi-slice CT, echocardiography, and V/P scintigraphy were performed in 75%, 55%, and 7% of the institutions, respectively. Echocardiography is the gold standard technique for the evaluation of right ventricular dysfunction in acute PTE cases. Right ventricular dysfunction is associated with early mortality and a poor clinical course (26, 27). When multi-slice CT cannot be performed due to hemodynamic disorder, bedside transthoracic echocardiography must be immediately taken in order to determine right ventricular dysfunction for the decision about emergent reperfusion treatment and to rule out other conditions (aortic dissection, acute coronary syndrome, pericardial tamponade, etc.) that can cause this picture. Intracardiac thrombus can sometimes be observed with this examination. A thrombotic event can be supported by bedside Doppler USG of the lower extremity. In our study, while both bedside echocardiography and Doppler USG were performed in 27.5% of the institutions, only echocardiography was performed in 34.5% and only Doppler USG was performed in 34.5%. In 3.1% of the institutions, none of them was performed.

Various clinical scoring systems are used for risk and prognostic evaluation. They help to predict complicated clinical courses, such as one-month early mortality, recurrence, and nonfatal major bleeding. The most recent of these is the pulmonary embolism severity index (PESI). Class I and class II in the PESI scoring have a high negative predictive value of 97% for the determination of patients that have a low risk of 30-day mortality and that can be given outpatient treatment (28). The simplified PTE severity index (sPESI), which is less complicated and has less parameters, has been found to be as efficient as PESI (29, 30). A value of sPESI=0 shows a low risk of a 30-day poor prognosis, whilea value of sPESI ≥1 shows a high risk. It has been stated in the guidelines that the outpatient therapy of anticoagulation can be started in patients with SPESI=0 or PESI class I-II PTE. Also in our study, 61.6% of the physicians specified that they preferred outpatient therapy in patients with a value of sPESI=0. In the study conducted by Özsu et al. (31), they suggested that patients with a negative troponin value and low sPESI score can be given outpatient therapy safely.

In our study, it was found that 77.3% of physicians applied thrombolytic therapy previously. As stated in the guidelines (4-6), while 86.2% of physicians preferred LMWH treatment in non-massive and submassive PTE patients, vitamin K antagonist was the most commonly used drug in maintenance treatment at the rate of 84.9%.

If the risk of bleeding is not high in patients having a high clinical suspicion, particularly in massive patients, LMWH, standard heparin or rivoroxaban, apixaban or endoxaban, which are direct factor Xa inhibitors from new oral anticoagulants, can be used until the exclusion of the diagnosis (32). If the diagnostic tests are expected to result in a time later than 4 hoursin the presence of a moderate clinical suspicion and in a time later than 24 hours in patients with a low clinical suspicion, anticoagulant therapy is recommended unless otherwise proven. In submassive PTE cases with right ventricular dysfunction detected in electrocardiography, the application of primary thrombolytic therapy is controversial, and, after risk evaluation, the initiation of rescue thrombolytic therapy is recommended in selected PTE cases, unless the risk of bleeding is high (32, 33). If there is no major

contraindication in massive PTE cases accompanied by hypotension and/or shock, thrombolytic treatment is applied. While the duration of treatment in patients firstdiagnosed with PTE (not associated with cancer and thrombophilia) was 3–6 months in 76.4% of the patients, it was 6–12 months in 23.6% of the patients. In the guidelines, the duration of treatment in PTE patients depending on temporary risk factors is recommended to continue for 3–6 months at a minimum level (4, 6).

After the completion of pulmonary thromboembolism treatment, while 78.7% of the physicians evaluated the level of D-dimer for assessing the occurrence of recurrence, 21.2% of them did not. Moreover, after the end of the treatment, 56.8% of the physicians always requested an imaging technique, while 32.5% sometimes requested one. The most commonly requested techniques were multi-slice CT (77.6%), echocardiography (48%), and Doppler USG (57.8%), respectively. In fact, the decision for stopping treatment through control CT is not recommended in any guidelines. CT can be requested in the case of suspected recurrence or CTEPH. In cases that are submassive/massive at the beginning and defined to have dyspnea in the follow-up, performing echocardiography is appropriate for PH. In one study conducted, it was concluded that negative D-dimer results obtained during follow-ups in patients having idiopathic VTE for the first time were not enough to discontinue the treatment (34). After stopping the treatment, the duration of follow-up was found to be 12 months by 33.4% of the physicians, 6 months in 25%, and 3 months in 14.5%. Of the physicians, 27% did not follow up. Kayaalp et al. (35) established the diagnosis of CTEPH in 5 of 99 PTE patients (5.5%) that were followed up for one year or a maximum of two years. Korkmaz et al. (36) diagnosed 4.6% of 325 patients, who were followed up for 16.3 months, with CTEPH. Furthermore, in the study of Korkmaz et al., chronic residual thrombus was observed in 48% of patients during the follow-up in the third month, in 27.4% of patients during the follow-up in the sixth month, and in 18.2% of patients during the follow-up at the end of twelve months. In line with these studies, it has been reported that the follow-up of PTE patients will be beneficial. The primary treatment in CTEPH is pulmonary endarterectomy in appropriate patients. In our study, although endarterectomy was not performed in 89.2% of the institutions, 81.2% of physicians stated that they recommended CTEPH patients to undergo endarterectomy.

In conclusion, we suggest that the fact that most of the examination techniques are used by institutions as well as clinical scoring systems and sPESI by many physicians increases the accordance with the guidelines. However, we also suggest that the fact that some examinations cannot be performed and interpreted immediately (under the conditions of shifts) decreases the level of this accordance. The limitation of our study is the low number of chest diseases physicians who participated in the questionnaire. However, we believe that the results reflect the general picture Turkey owing to the participation from many cities, universities, and public and education hospitals.

CONCLUSION
In our study, the non-existence of examination techniques used for the diagnosis of PTE in some institutions and the difficulty in reaching available tests at any time of a day were remarkable points. In particular, restricted accessibility to some assays such as the high-sensitivity D-dimer test and bedside echocardiography used for evaluating

Anar et al. Approaches of Physicians for Pulmonary Thromboembolism

Eurasian J Pulmonol 2016; 18: 96-103

right ventricular dysfunction, troponin, and NT-pro-BNP is suggested to decrease the accordance with the guidelines.

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