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Prognostic importance of central thrombus in hemodynamically stable patients with pulmonary embolism

Aysegul Senturk[1], Savas Ozsu[2], Serap Duru[3], Ebru Cakır[4], Sevinc Sarinc Ulaslı[5], Ezgi Demirdogen[6], Servet Kayhan[7], Aygul Guzel[8], Fatih Yakar[9], Serdar Berk[10]; on behalf of The TUPEG Study Investigators

[1]Ankara Atatürk Training and Research Hospital, Department of Pulmonary Medicine, Ankara, Turkey
[2]Karadeniz Technical University, School of Medicine, Department of Pulmonary Medicine, Trabzon, Turkey
[3]Ankara Dışkapı Training and Research Hospital, Department of Pulmonary Medicine, Ankara, Turkey
[4]Trakya University, School of Medicine, Department of Pulmonary Medicine, Edirne, Turkey
[5]Afyon Kocatepe University, School of Medicine, Department of Pulmonary Medicine, Afyon, Turkey
[6]Uludağ University, School of Medicine, Department of Pulmonary Medicine, Bursa, Turkey
[7]Recep Tayyip Erdoğan University, School of Medicine, Department of Pulmonary Medicine, Rize, Turkey
[8]19 Mayıs University, School of Medicine, Department of Pulmonary Medicine, Samsun, Turkey
[9]Bezmi Alem University, School of Medicine, Department of Pulmonary Medicine, İstanbul, Turkey
[10]Cumhuriyet University, School of Medicine, Department of Pulmonary Medicine, Sivas, Turkey

Abstract

Background: *The association between mortality and localization of central thrombus in hemodynamically stable patients with pulmonary embolism (PE) is unclear. Sufficient data are not available to help clinicians to select between low molecular weight heparin (LMWH), unfractionated heparin (UFH) and thrombolytics for the management of central thrombus. The present study aims to investigate whether central thrombus in the pulmonary artery affects 30-day mortality rate, and to compare the outcomes of different treatment approaches in patients with central thrombus.*

Methods: *This multi-central, prospective, observational study included 874 hemodynamically stable patients with PE confirmed by multidetector computed tomography scan. The localization of the emboli was evaluated and categorized as central (saddle or at least one main pulmonary artery), lobar or distal. The primary study outcome was 30-day all-cause mortality.*

Results: *Localization of the emboli was central in 319 (36.5%) patients, lobar in 264 (30.2%) and distal in 291 (33.2%) patients. Seventy-four (8.5%) patients died during the 30-day follow-up period. All-cause mortality rate was 11.9%, 6.8% and 6.2% in patients with central, lobar, and distal emboli, respectively ($p < 0.001$). Multivariate analysis did not show that hemodynamically stable central thrombus was an independent predictor of mortality. Additionally, mortality rate was not significantly different between UFH, LMWH and thrombolytic therapy groups.*

Conclusions: *The present study showed that central thrombus was not an independent predictor of mortality in hemodynamically stable PE patients. LMWH and UFH were similarly effective in the treatment of this patient group.* (Cardiol J 2017; 24, 5: 508–514)

Key words: pulmonary embolism, multidetector computed tomography, central thrombus, anticoagulation, mortality

Address for correspondence: Dr. Aysegul Senturk, Ankara Atatürk Training and Research Hospital, Department of Pulmonary Medicine, 06800, Ankara, Turkey, tel: +90 312 2912525, fax: +90 312 2912529, e-mail: asenturk1967@yahoo.com

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Introduction

The clinical signs of pulmonary embolism (PE) vary from silent or very mild symptoms to massive findings that result in sudden death [1]. Previous reports showed that the level of vascular occlusion, number, size and location of the emboli, and patient's age and comorbidities are the most important determinants of the severity of patient signs and symptoms. Defining the appropriate treatment protocols based on risk stratification is essential in preventing complications in patients with suspected PE [2]. On the other hand, delays in diagnosis or inaccurate risk stratification may result in serious morbidity and mortality.

A prompt and efficient risk stratification of patients is crucial in PE treatment. Although echocardiography and cardiac biomarkers play important roles in diagnosis and risk stratification based on clinical history of normotensive PE patients, many of these markers still do not have large clinical availability and clinicians continue to seek more accurate means of risk stratification [2]. Recent advances in multi-detector computed tomography (MDCT) have significantly improved our ability to diagnose fatal PE.

Since mortality rate is high among patients with massive embolism and unstable hemodynamic findings, it is indisputable that these patients must be provided with rapid and aggressive treatment. However, mortality rate in normotensive patients with central thrombosis is unclear and sufficient data are not available to help the clinicians to select between different treatment options, such as with low molecular weight heparin (LMWH), unfractionated heparin (UFH) and thrombolytics [3].

The present study aims to investigate whether central thrombus in the pulmonary artery affects 30-day mortality rate, and to compare the outcomes of different treatment approaches in patients with central thrombus.

Methods

Study design

This study was conducted between January 2013 and June 2013, as part of a large prospective multi-center study carried out in 66 study centres in Turkey. Data prospectively collected from patients enrolled to the Turkey Pulmonary Embolism Groups (TUPEG) were assessed in this study [4]. The study population consisted of 874 patients with PE diagnosed by MDCT scan. Written informed consent was obtained from all patients and the study protocol was approved by the local ethics committee of the coordinating centre (Approval Number: 173/2012).

Patients and setting

The study population consisted of 874 patients who were admitted with normotensive acute PE. Demographic characteristics, clinical and laboratory data of all patients were obtained from the electronic databases of the participating hospitals. Well score for PE was calculated for each patient. Laboratory parameters (D-dimer, high sensitive troponin-I or troponin-T, natriuretic peptides) were analysed according to local standards. The recorded comorbidities included history of venous thromboembolism (VTE), malignancy, chronic obstructive pulmonary disease (COPD), coronary artery disease, cerebrovascular disease and congestive heart failure.

Severity of pulmonary embolism was classified in three groups according to the European Society of Cardiology guidelines as follows: high-risk (patients with shock or hypotension); intermediate-risk (presence of a positive marker for myocardial injury or right ventricular dysfunction [RVD]); low-risk (absence of RVD or negative marker of myocardial injury) [5]. PE patients with shock or hypotension (high risk defined by the ESC as systolic blood pressure of 90 mm Hg or a pressure drop of ≥ 40 mm Hg for 15 min if not caused by new onset arrhythmia) were excluded from the study.

MDCT scan was performed in all patients and assessed for localization of the thrombus. Thrombus localization was evaluated and categorized as follows: central (saddle or at least one main pulmonary artery), lobar and distal (segmental or subsegmental pulmonary arteries).

Study outcome

The primary study outcome was 30-day all-cause death or clinical deterioration in hemodynamically stable patients with central thrombus. The secondary outcomes included all-cause mortality, non-fatal symptomatic re-embolism VTE, and non-fatal major haemorrhage.

Statistical analyses

Statistical analyses were performed with the SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was applied to determine probability distribution. Data were reported as percentages, means ± standard deviations (SD) and medians, where appropriate. Kruskal Wallis test was used for inter-group com-

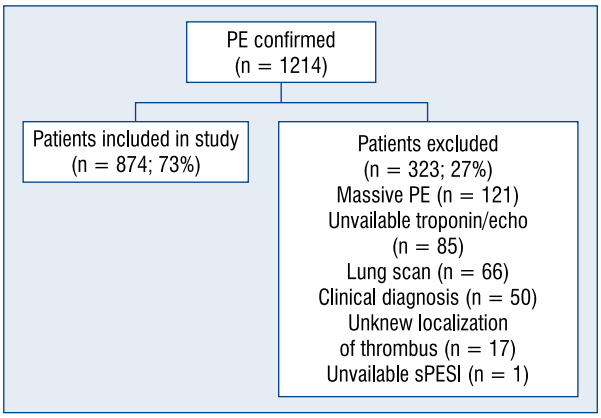

Figure 1. Patient study eligibility; PE — pulmonary embolism; sPESI — simplified pulmonary embolism index.

parisons and discrete variables were compared by the χ^2 test. P values < 0.05 were considered statistically significant in all analyses. All factors with potential effects on 30-day mortality were further investigated by univariable screening. Subsequently, all parameters found to be associated with 30-day mortality at a significance level lower than 0.1 were analyzed in a stepwise multivariable Cox regression analysis. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs).

Results

A total number of 1214 patients with acute PE were evaluated. Of these, 340 (27%) were excluded because MDCT-scanning was not performed or because the patients were not available for echocardiography and/or troponin measurements and 121 patients were excluded because they were not hemodynamically stable (Fig. 1).

The median age at diagnosis was 67 ± 16.8 years (range 19–96 years), and 350 (46.5%) patients were male. Localization of emboli was central in 319 (36.5%) patients, lobar in 264 (30.2%) and distal in 291 (33.2%) patients. There was no correlation between localization of emboli and sex or age. In terms of comorbidities, 79 (9%) patients had cardiopulmonary disease, 54 (6.2%) had COPD, 62 (7%) had congestive heart failure, 36 (4.1%) had history of ischemic stroke, and 88 (10.1%) patients had history of cancer.

The most common symptom at presentation was dyspnoea (85%), followed by chest pain (47%), haemoptysis (12%) and syncope (6%). No risk factor was recorded in 173 (20%) cases. Patient characteristics are shown in Table 1.

Table 1. Characteristic features of patients included in the study.

	Number of patients (%)
Demographic features	
Sex: females/males (% female)	468/406 (53.5%)
Median age [years]	67 (19–96)
Median SBP [mm Hg]	120 (90–210)
Median SaO_2 [%]	92 (69–99)
Risk factors	
Immobilization	236 (27.0%)
Recent surgery	114 (13.0%)
Cancer	88 (10.0%)
Idiopathic	176 (20.0%)
Symptoms at presentation	
Dyspnea	745 (85.2%)
Chest pain	413 (47.3%)
Hemoptysis	106 (12.1%)
Syncope	54 (6.2%)
Localization of thrombus	
Central	319 (36.5%)
Lobar	264 (30.2%)
Distal	291 (33.2%)
Co-morbid disease	
Cardiopulmonary disease	79 (9.0%)
COPD	54 (6.2%)
Congestive heart failure	62 (7.0%)
Ischemic stroke	36 (4.1%)
Cancer	88 (10.1%)

COPD — chronic obstructive pulmonary disease; SBP — systolic blood pressure, SaO_2 — oxygen saturation of arterial blood

Univariate analysis showed that RVD on echocardiography (OR: 2.57, 95% CI: 1.85–3.48, $p < 0.001$) as well as elevated serum troponin levels (OR: 1.92, 95% CI: 1.43–2.60, $p < 0.001$) were independent predictors of mortality. Troponin concentration was found to be related to the location of the largest visible embolus ($p < 0.001$); the highest concentrations were measured in patients with central thrombus and the lowest concentrations were detected in the lobar-distal group. Elevated troponin levels at presentation were more common in patients with RVD ($p < 0.001$) as well as central thrombi on MDCT scan (Table 2).

Syncope was present in 29 (54%) patients with central, 13 (24%) patients with lobar and 12 (22%) patients with distal emboli. Univariate analysis evaluating the presence of syncope with respect

Table 2. Medical conditions and symptoms at presentation and according to the localization of thrombus.

	Central (n = 319)		Lobar (n = 264)		Distal (n = 291)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Respiratory rate [min]	1.03 (1.00–1.05)	0.015	0.98 (0.95–1.00)	0.13	0.98 (0.96–1.01)	0.28
Pulse [min]	1.01 (1.00–1.01)	0.003	0.99 (0.98–1.00)	0.19	0.99 (0.98–1.00)	0.67
RVD	2.57 (1.85–3.48)	0.000	1.05 (0.77–1.42)	0.74	0.35 (0.26–0.48)	< 0.0001
Elevated troponin levels	1.92 (1.43–2.60)	< 0.0001	0.78 (0.57–1.08)	0.14	0.60 (0.44–0.83)	0.002
SaO_2 [%]	0.98 (0.96–0.99)	0.026	1.00 (0.98–1.01)	0.96	1.02 (1.00–1.04)	0.024
Age > 75	1.28 (0.94–1.74)	0.110	0.73 (0.52–1.02)	0.07	1.02 (0.74–1.39)	0.90
Syncope	2.15 (1.23–3.74)	0.007	0.69 (0.36–1.32)	0.27	0.56 (0.29–1.08)	0.085
Concomitant DVT	1.26 (0.95–1.66)	0.09	0.95 (0.71–1.27)	0.72	0.81 (0.61–1.09)	0.17
30-day mortality	1.9 (1.2–3.1)	0.006	0.7 (0.4–1.2)	0.25	0.62 (0.3–1.0)	0.08

OR — odds ratio; CI — confidence interval; RVD — right ventricular dysfunction; SaO_2 — oxygen saturation of arterial blood; DVT — deep venous thrombosis

to thrombus localization demonstrated that syncope was statistically significantly twice as often among patients with central thrombus (OR 2.15, 95% CI: 1.23–3.74, $p < 0.007$). Conversely, there was no relation between lobar (OR 0.69, 95% CI: 0.36–1.32, $p > 0.05$) or distal (OR: 0.56, 95% CI: 0.29–1.08, $p > 0.05$) localization of thrombi and presence of syncope.

Seventy-four (8.5%) patients died during the 30-day follow-up period. The rate of all-cause mortality was 11.9%, 6.8% and 6.2% in patients with central, lobar, and distal emboli, respectively. The 30-day mortality rate was higher among patients with central thrombus, compared to those with lobar or distal thrombus ($p < 0.001$) (Fig. 2). Although Cox analysis showed that the presence of thrombus in the main pulmonary artery significantly increased the mortality rate (OR: 2.0. 95% CI: 1.2–3.3, $p = 0.007$), multivariate Cox analysis did not show statistical significance (Table 3).

Among patients with central thrombus, 86 (27%) were given UFH, 198 (62.1%) were given LMWH and 34 (10.7%) were administered tissue plasminogen activator therapy.

Mortality rates of patients with thrombus in the main pulmonary artery did not significantly differ between the heparin (OR: 1.7, 95% CI: 0.8–3.6, $p > 0.05$) and LMWH (OR: 0.9, 95% CI: 0.4–1.9, $p > 0.05$) treatment groups. Use of thrombolytic agents also did not decrease the mortality rate in this patient group (Table 4).

Among PE patients with central thrombus, the number of patients with high risk simplified pulmonary embolism index (sPESI) was higher than those with low risk sPESI (26.5% and 41.3%, respectively) (Table 5).

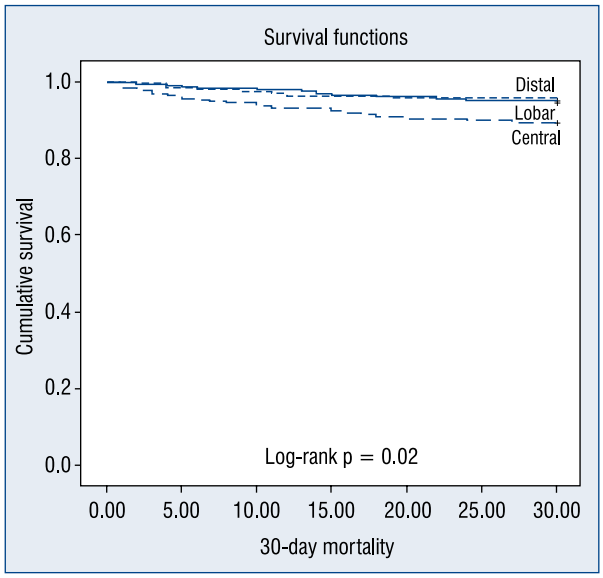

Figure 2. Cumulative risk of death in the study population according to localization of thrombus.

Table 3. In multivariable Cox's regression analysis for 30-day all cause mortality in normotensive patients with pulmonary embolism.

Localization of thrombus	OR	95% CI	P
Central	1.01	1.0–1.02	NS
RVD on echo	0.80	0.46–1.54	NS
Positive troponin	2.8	1.50–5.10	0.001
High risk sPESI	5.0	1.74–14.10	0.003

OR — odds ratio; CI — confidence interval; NS — non-significant; RVD — right ventricular dysfunction; sPESI — simplified pulmonary embolism index

Table 4. 30-day mortality according to different treatment regimens in central thrombus by univariable Cox's analysis.

	P	OR	95% CI	
			Lower	Upper
Unfractionated heparin	NS	1.482	0.720	3.048
Thrombolytic therapy	NS	0.203	0.027	1.530
Low molecular weight heparin	NS	1.054	0.523	2.127

Values are given in percent and 95% confidence interval (CI); OR — odds ratio; NS — non-significant

Table 5. The relationship between the central thrombosis and simplified pulmonary embolism index (sPESI).

	sPESI (+)	sPESI (–)
Central thrombus (+)	244 (41.3%)	75 (26.5%)
Central thrombus (–)	347 (58.7%)	208 (73.5%)

Kaplan-Meier analysis assessing the 30-day mortality rates with respect to the localization of thrombus did not establish any statistically significant difference (Fig. 2).

Discussion

Although the present study demonstrated that 30-day mortality rate was increased in hemodynamically stable PE patients with central thrombus diagnosed by MDCT, multivariate analysis did not show a significant impact of thrombus localization on 30-day mortality. Troponin levels however, were significantly increased and RVD determined by echocardiography was more common among patients with central thrombus. Another very important finding of this study was the similarity between the efficacies of LMWH and UFH in the treatment of patients with central thrombus.

It is commonly known that risk stratification is essential to tailor the appropriate treatment modalities in PE patients. The localization of emboli as determined by MDCT angiography has been suggested to be useful for risk stratification in hemodynamically stable patients with acute PE [6, 7]. A recent meta-analysis including 5 studies and 2215 patients demonstrated an association between localization of thrombus in central arteries and 30-day mortality [8].

Data available in the literature concerning the prognosis of patients with central PE are controversial. Klok et al. [9] demonstrated central thrombi in 28% of 674 PE patients, and they suggested that central localization of thrombus does not affect mortality within 90 days. In one previous study, no effect was detected of central thrombus on the rate of mortality in hemodynamically stable patients with PE [10]. In another study, central thrombus was shown to be an independent predictor of all-cause death or clinical deterioration in hemodynamically stable patients ($p = 0.047$). Clinical deterioration was arterial hypotension requiring catecholamine infusion, endotracheal intubation, worsening symptoms and respiratory failure or recurrent PE [11]. In that study however, thrombus localization was central in the majority of cases (60%) and the reported p value was borderline significant [12]. In the present study, thrombus was centrally localized in a relatively small number of patients (37%).

In the present study, it was demonstrated that RVD determined by echocardiography was more common in patients with central thrombus. This is not necessarily a reason for a greater right ventricular afterload, as was also determined the peripheral microembolisms may have resulted in a major increase in pulmonary vascular resistance [13, 14]. Especially in patients with widespread thrombus, rapid hemodynamic collapse may be observed before adaptation in the right ventricle and syncope can be defined as an important clinical finding of this condition. In this study, syncope was twice as common among patients with central thrombus. Similarly, Berghaus et al. [15] reported the presence of central thrombus as an independent risk factor for RVD on echocardiography. Conversely, one meta-analysis found that the mortality rate was increased by 1.8 fold in patients with RVD determined by CT [8].

Cardiac troponins are the most specific and sensitive markers of myocardial necrosis and myocardial cellular damage. Troponin increase was shown to be a marker of RVD and was associated with elevated early mortality rates in cases with acute PE [16, 17]. However, the relation between troponin levels and localization of the emboli has not been sufficiently investigated. In patients with non-massive central PE who were admitted to the emergency room, increased troponin I levels were shown to be useful in identifying those with high risk of developing hemodynamic instability, independent of a clinically-based risk score [18]. In this study, cases with central thrombus had statistically

significantly higher troponin levels and frequent signs of RVD on echocardiography, compared to cases with distal thrombus. It was also revealed that an elevated troponin level was an independent predictor of mortality.

According to this research thus far, no study has demonstrated an association between central thrombus and sPESI. In the present study, patients with high risk sPESI more often had central thrombus. This may be explained by the presence of sPESI criteria such as tachycardia and desaturation, which are more commonly observed among patients with central thrombus.

Studies investigating poor prognosis in patients with central thrombus reported limited data on the choice of anticoagulants. In cases where the presence of a central thrombus is considered to be a sign of RVD, it can be recommended to categorize these patients to submassive/intermediate risk groups. On the other hand, use of thrombolytic treatment in submassive PE is still controversial [19, 20]. However, UFH is preferred during the initial stage of massive PE and therefore, it can be concluded that UFH may be more effective in cases with central thrombus. The present study showed that there was no significant difference between UFH and LMWH in terms of efficacy. Since the study is not randomize controlled study (RCT), the view put forward herein is an assumption. To prove this, RCT work is needed. Moreover, mortality rate did not change with thrombolytic treatment in hemodynamically stable cases with central thrombus. In a previous study, Hamel et al. [21] compared thrombolytics and heparin therapy in patients with submassive and demonstrated greater improvement on perfusion lung scans of the patients treated with thrombolytics compared to those treated with heparin. In that study however, the in-hospital mortality rate was 6.25% in the thrombolytic group and 0.0% in the heparin group [21]. On the other hand, a recent meta-analysis of 7 studies including a total number of 594 patients reported that the cumulative effect of thrombolysis did not result in a statistically significant difference in mortality compared to intravenous heparin therapy [22].

Clinical findings of the present study can be summarized as follows: 1) No differences were observed with regard to mortality when UFH and LMWH treatments were compared; 2) Although the presence of central thrombus was not found to be an independent predictor of mortality, it can be concluded that ideally these patients should be treated in hospital settings since central thrombus is more commonly associated with RVD and elevated troponin levels. On the other hand, it has been previously suggested that distal embolism in hemodynamically stable patients can be treated in an outpatient setting [23].

Limitations of the study

This study has some limitations. Firstly, pulmonary occlusion index or right ventricle/left ventricle ratios on CT were not calculated. In addition, when interpreting the results of the present study, one should consider that no autopsy was performed. Moreover, each study centre used different scans of multi-slice CTs. Nevertheless, it was believed to not have affected localization of the thrombus (central, lobar, distal).

Conclusions

In conclusion, the present study demonstrated that 30-day mortality rate was higher in patients with central thrombus compared to the other patients. However, hemodynamically stable central thrombus was not found to be an independent predictor of mortality.

On behalf of The TUPEG Study Investigators

Nalan Demir, Tevfik Ozlu, Elif Yilmazel Ucar, Gamze Kırkıl, Esra Ekbic Kadıoglu, Bülent Altınsoy, Bengü Saylan, Hatice Selimoglu Sen, Gul Dabak, Nuri Tutar, Ahmet Uysal, Hayriye Bektas, Gulbahar Darılmaz, Nilgun Yilmaz Demirci, Fusun Alatas, Funda Coskun, Sulhattin Arslan, Fatmanur Karakose, Selami EkinİsmailSavas, Umran Topu, Erdogan Cetinkaya, Dursun Tatar, Tulin Kuyucu, Ozlem Kar Kurt, Nagehan Durmus, Pınar Yıldız, Aydanur Ekici, Murat Acat, Serhat Celikel, Mehmet Yavsan, Sibel Arınc, Ayşe Bahadır, Nesrin Mogulkoc, Ersin Gunay, Seyma Baslılar

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References

1. Giancarlo A, Becattini C. Acute pulmonary embolism. N Engl J Med. 2010; 363(19): 266–274, doi: 10.1056/NEJMra0907731.
2. Paiva L, Barra S, Providência R. Pulmonary embolism risk stratification: where are we heading? Eur Respir J. 2014; 43(1): 298–300, doi: 10.1183/09031936.00036113, indexed in Pubmed: 24381322.
3. Fei J, Tang Y, Wu J, et al. Thrombolytic and anticoagulant therapy for acute submassive pulmonary embolism. Exp Ther Med. 2014; 7(1): 103–108, doi: 10.3892/etm.2013.1355, indexed in Pubmed: 24348773.
4. Ozsu S, Ozlu T, Sentürk A, et al. TUPEG Study Investigators. Combination and comparison of two models in prognosis of pulmonary

embolism: results from TUrkey Pulmonary Embolism Group (TUPEG) study. Thromb Res. 2014; 133(6): 1006–1010, doi: 10.1016/j.thromres.2014.02.032, indexed in Pubmed: 24690480.
5. Torbicki A, Perrier A, Konstantinides S, et al. ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008; 29(18): 2276–2315, doi: 10.1093/eurheartj/ehn310, indexed in Pubmed: 18757870.
6. Jiménez D, Lobo JL, Monreal M, et al. PROTECT investigators. Prognostic significance of multidetector CT in normotensive patients with pulmonary embolism: results of the protect study. Thorax. 2014; 69(2): 109–115, doi: 10.1136/thoraxjnl-2012-202900, indexed in Pubmed: 23525079.
7. Özsu S, Kırış A, Bülbül Y, et al. Relationship between cardiac troponin-T and right ventricular Tei index in patients with hemodynamically stable pulmonary embolism: an observational study. Anadolu Kardiyol Derg. 2012; 12(8): 659–665, doi: 10.5152/akd.2012.218, indexed in Pubmed: 22968301.
8. Vedovati MC, Germini F, Agnelli G, et al. Prognostic role of embolic burden assessed at computed tomography angiography in patients with acute pulmonary embolism: systematic review and meta-analysis. J Thromb Haemost. 2013; 11(12): 2092–2102, doi: 10.1111/jth.12429, indexed in Pubmed: 24134450.
9. Klok FA, Djurabi RK, Nijkeuter M, et al. High D-dimer level is associated with increased 15-d and 3 months mortality through a more central localization of pulmonary emboli and serious comorbidity. Br J Haematol. 2008; 140(2): 218–222, doi: 10.1111/j.1365-2141.2007.06888.x, indexed in Pubmed: 18028485.
10. Ozsu S, Karaman K, Mentese A, et al. Combined risk stratification with computerized tomography /echocardiography and biomarkers in patients with normotensive pulmonary embolism. Thromb Res. 2010; 126(6): 486–492, doi: 10.1016/j.thromres.2010.08.021, indexed in Pubmed: 20920821.
11. Konstantinides S, Geibel A, Heusel G, et al. Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002; 347(15): 1143–1150, doi: 10.1056/NEJMoa021274, indexed in Pubmed: 12374874.
12. Vedovati MC, Becattini C, Agnelli G, et al. Multidetector CT scan for acute pulmonary embolism: embolic burden and clinical outcome. Chest. 2012; 142(6): 1417–1424, doi: 10.1378/chest.11-2739, indexed in Pubmed: 22628491.
13. Wanless RB, Anand IS, Poole-Wilson PA, et al. Haemodynamic and regional blood flow changes after acute pulmonary microembolism in conscious rabbits. Cardiovasc Res. 1988; 22(1): 31–36, indexed in Pubmed: 3167926.
14. Perkett EA, Brigham KL, Meyrick B, et al. Continuous air embolization into sheep causes sustained pulmonary hypertension and increased pulmonary vasoreactivity. Am J Pathol. 1988; 132(3): 444–454, indexed in Pubmed: 3414777.
15. Berghaus TM, Haeckel T, Behr W, et al. Central thromboembolism is a possible predictor of right heart dysfunction in normotensive patients with acute pulmonary embolism. Thromb Res. 2010; 126(3): e201–e205, doi: 10.1016/j.thromres.2010.06.009, indexed in Pubmed: 20638710.
16. Becattini C, Agnelli G. Acute pulmonary embolism: risk stratification in the emergency department. Intern Emerg Med. 2007; 2(2): 119–129, doi: 10.1007/s11739-007-0033-y, indexed in Pubmed: 17619833.
17. Masotti L, Righini M, Vuilleumier N, et al. Prognostic stratification of acute pulmonary embolism: focus on clinical aspects, imaging, and biomarkers. Vasc Health Risk Manag. 2009; 5(4): 567–575, indexed in Pubmed: 19649307.
18. Palmieri V, Gallotta G, Rendina D, et al. Troponin I and right ventricular dysfunction for risk assessment in patients with nonmassive pulmonary embolism in the Emergency Department in combination with clinically based risk score. Intern Emerg Med. 2008; 3(2): 131–138, doi: 10.1007/s11739-008-0134-2, indexed in Pubmed: 18270791.
19. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost. 2014; 12(4): 459–468, doi: 10.1111/jth.12521, indexed in Pubmed: 24484241.
20. Worster A, Smith C, Silver S, et al. Evidence-based emergency medicine/critically appraised topic. Thrombolytic therapy for submassive pulmonary embolism? Ann Emerg Med. 2007; 50(1): 78–84, doi: 10.1016/j.annemergmed.2007.01.002, indexed in Pubmed: 17449142.
21. Hamel E, Pacouret G, Vincentelli D, et al. hrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. Chest. 2001; 120(1): 120–125, indexed in Pubmed: 11451826.
22. Cao Y, Zhao H, Gao W, et al. Systematic review and meta-analysis for thrombolysis treatment in patients with acute submassive pulmonary embolism. Patient Prefer Adherence. 2014; 8: 275––282, doi: 10.2147/PPA.S56280, indexed in Pubmed: 24611003.
23. Ucar EY, Araz O, Akgun M, et al. Low-molecular-weight heparin use with thrombolysis: is it effective and safe? Ten years' clinical experience. Respiration. 2013; 86(4): 318–323, doi: 10.1159/000346203, indexed in Pubmed: 23406693.