

Comparison of death risk stratification criteria in pulmonary embolism based on the estimation of pulmonary arterial bed occlusion

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Summary

Objective

To clarify angiographic criteria of massive pulmonary thrombotic masses for stratification of the risk of death in patients with pulmonary embolism according to the recommendations of the European society of cardiology (2014).

Material and methods

We analyzed the volume of pulmonary lesions in 371 patients with pulmonary embolism with different risk of early death according to the criteria of the European society of cardiology (2014)

Results

It was found that patients with high, moderately high, and moderately low risk of death from pulmonary embolism did not differ significantly in the volume and degree of obstruction of the arteries of the small circle of blood circulation. Early death risk stratification is most accurate when patients were hospitalized on the first day of the development of symptoms of the disease. At this time, the most informative indicators were plasma concentration of troponin and brain natriuretic peptide that came back to normal levels after 3 and 5 days, respectively. When patients were admitted to hospital at a later date, these laboratory indicators were not specific for the stratification of the risk of death. This leads to undervalued assessment of the risk of death in this category of patients, and

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therefore it may cause not enough adequate choice of tactics of management of these patients. Estimation of the volume of pulmonary bed thrombotic occlusion could be useful to neutralize this difference between the groups can estimate the volume of thrombotic occlusion of the pulmonary bed. Total absence of blood flow in 10 or more segmental arteries was critical for manifestation of clinical, ECG and EchoCG symptoms of volumetric overload of the right heart.

Conclusion

The total absence of blood flow in 10 or more segmental arteries is comparable with occlusion of one main pulmonary artery and can be treated as a massive lesion of the small circle of blood circulation. The application of this assessment of pulmonary lesions severity in pulmonary embolism is not inferior to the classification proposed by the European society of cardiology in 2014 due to high prevalence of all criteria used in this classification.

Keyword

Pulmonary embolism, massive lesions, segmental arteries.

Introduction

Pulmonary embolism (PE) is the occlusion of pulmonary artery branches with thrombotic masses that often leads to patient's death [1, 2, 3]. According to epidemiological data, this disease is diagnosed in 0.15-0.20% of the world population [4]. Around 2 000 000 and 700 000 cases of PE are registered in the USA and Europe every year. PE frequency in Russia is 35-40 cases for 100 000 persons per year [1, 3, 5]. Total mortality rate in PE reaches 30% [5, 6]. But well-timed diagnostics and adequate therapy allow to keep this number as low as 3% [7, 8].

Nowadays the stratification of the European society of cardiology (ESC) (2014) including groups of high, moderate and low risk of death is used for optimization of PE treatment [3]. Distribution of patients into these groups is based on clinical manifestations and results of laboratory and instrumental tests. In addition, Pulmonary Embolism Severity Index (PESI) and its modification sPESI are taken into consideration [9, 10].

This classification does not consider the volume of pulmonary vessels occluded by thrombi and excluded from circulation. It is particularly important for patients with moderately-high risk of death since these patients can receive both systemic thrombolytic therapy and anticoagulant treatment [11, 12]. In these cases, the severity of thrombotic lesion of the arteries of the pulmonary circulation can play a crucial role.

It is common to evaluate the level of lesion of the pulmonary arteries by the proximal level of occlusion. However, often CT angiopulmonography detects an incomplete obturation of the lumen of the pulmonary artery branches of any order. This type of lesion, even in the presence of thrombotic masses in the main pulmonary arteries, often does not lead to

evident hemodynamic disturbances. [13, 14]. In these patients, a large number of thrombotic masses occluding smaller arteries like lobar and segmental ones is present.

The objective of the study is to detailize the criteria of massive pulmonary thrombotic masses taking into account CT results to clarify the criteria for stratification of death risk in patients with PE according to the recommendations of the ESC (2014).

Materials and methods

371 patients were admitted to the National Pirogov Medical Surgical Center during the period from 2005 to 2017. 195 patients were males, and 176 patients were females. Age of patients varied from 23 to 95 years, the average age was 56.3±16.1 years.

The distribution of the proximal level of pulmonary artery branches occlusion was the following: main pulmonary arteries – 8.4%, lobar pulmonary arteries – 60.6%, segmental arteries – 31%.

All patients underwent general clinical and biochemical blood tests, including determining the level of plasma concentrations of D-dimer, troponin I, brain natriuretic peptide (NT-Pro-BNP), electrocardiography (ECG), echocardiography (EchoCG), and Doppler ultrasound exam of lower extremity veins. All patients underwent Final TE diagnosis was established with CT-angiopulmonography.

The study was carried out in 2 stages. The first step was to determine the group of patients according to the risk of early death related to PE based on the criteria of the ESC (2014). Subsequently, the groups of high, moderately high, moderately low, and low risks of death were identified.

High risk of PE-related death was found in 31 patients. Between them there were 16 men and 15

women. Patients' age varied from 23 to 86 years, average age was 54.5 ± 20.2 years.

Moderately high risk of early death was present in 37 patients with PE, aged from 29 to 78 years, their average age was 59.8 ± 14.6 years. Between them there were 20 males and 17 females.

Moderately low risk of PE-associated death was detected in 52 patients (24 males, 28 females). Their age varied from 28 to 86 years, and their average age was 59.4 ± 14.9 years.

Low PE-associated death risk was found in 251 patients (135 males, 116 females). Their age varied from 28 to 95 years, average age was 55.5 ± 16.3 years.

CT angiopulmonography revealed that patients with PE of the large arteries often had not occlusion, but different degree of parietal thrombosis of the pulmonary arteries narrowing the vessel lumen. Embolic occlusion in these patients was usually located in more distal arteries. In case of parietal thrombosis of the main arteries occlusion could be found in lobar or segmental arteries. The lesions of several lobar arteries were frequently present in patients that led to impaired circulation in corresponding segmental arteries. Taking this into account, we consider necessary to evaluate the presence of thrombotic masses not in proximal (main and lobar) arteries but total reduction of circulation in distal (lobar and segmental) arteries. It is known that pulmonary arterial system consists of 20 segmental arteries. Consequently, the occlusion of main pulmonary artery leads to exclusion of 10 segmental arteries from the circulation. Lesions of such dimensions lead to pronounced hemodynamic abnormalities.

We tested this idea in patients with high, moderately high, and moderately low risk of PE-associated death. It was found that the volume of pulmonary lesions that considered total absence of circulation in segmental arteries was almost identical and its average values were 13.1 ± 2.8 , 12.9 ± 2.6 , 11.4 ± 1.5 , respectively.

At the second stage of this study we selected groups of patients depending on the total absence of circulation in the segmental arteries to clarify the assumption that significant hemodynamic disturbances corresponding to massive PE occur in the total absence of circulation in 10 or more segmental arteries. Considering this, all PE patients with different risk of early death were divided into 2 subgroups.

The first group included patients ($n=143$, 75 males, 68 females) with massive pulmonary artery lesions and total absence of circulation in 10 and more seg-

mental arteries (11.6 ± 1.3 arteries, massive PE). Patients' age varied from 23 to 85 years, their average age was 56.2 ± 15.4 years. The group of massive PE in 76.2% of cases was present with patients with high, moderately high or moderately low risk of PE-associated death.

The second subgroup (non-massive PE) included patients ($n=228$, 121 males, 107 females) with total absence of circulation in less than 10 segmental arteries (2.9 ± 2.4 in average). Patients' age varied from 27 to 95 years, their average age was 56.1 ± 16.5 years.

We compared the results of the first and the second group. In all groups the volume of thrombotic lesions of pulmonary artery branches assessed with CT-angiopulmonography was compared with the results of EchoCG, ECG, and clinical manifestations of these patients.

Results and discussion

The level of proximal occlusion with thrombotic masses was evaluated in patients with PE and different grades of early death risk and severity of pulmonary artery lesions using CT-angiopulmonography (Figure 1).

Proximal occlusion of pulmonary artery branches was found with comparable frequency in patients with massive PE and patients with high, moderately high and moderately low risk of early PE-related death according to the criteria of the ESC (2014) ($p > 0.05$). No patient with non-massive PE had occlusion of the main pulmonary artery. In this group lobar artery occlusion was statistically more frequent than in patients with the low risk of PE-associated death ($p < 0.01$). 82.4% of patients had occlusion of one lobar artery, 17.6% of patients had occlusion of two arteries one of which was superior or middle lobar artery of the right lung, consequently, total absence of circulation in segmental arteries in these patients did not exceed 9 arteries of this level.

Thus, we can assume that evaluation of the volume of pulmonary lesions with total absence of blood supply in 10 and more segmental arteries is comparable with high and moderate risk of PE-associated death, whereas absence of circulation in less than 10 segmental arteries corresponds to the low risk of early death. It was proved with correlation analysis that revealed significant correlation of this volume of lesions with high ($r=0.54$), moderately high ($r=0.68$) risk of early death from PE, and moderate degree correlation with moderately-low risk of death ($r=0.42$).

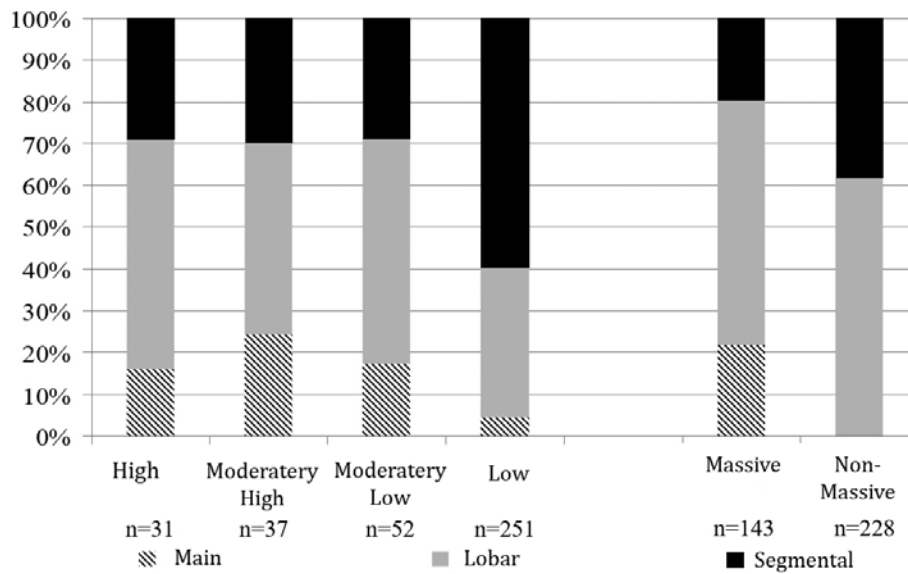


Figure 1. Distribution of the level of proximal occlusion of pulmonary artery branches in patients with PE.

Comment: Subgroups of patients: high death risk (n=31); moderatelyA high death risk (n=37); moderately low death risk (n=52); low death risk (n=251); Massive PE: total absence of circulation in 10 or more segmental arteries (n=143); Non-massive PE: total absence of circulation in less than 10 segmental arteries (n=228).

Table 1. The frequency of EchoCG criteria in PE patients with different early death risk

EchoCG parameter	Group of patients						P ₁	P ₂	P ₃	P ₄
	The risk of PE-associated death according to the ESC criteria (2014)				Considering total absence of circulation in segmental arteries					
	High risk n=31	Moderately high risk n=37	Moderately low risk n=52	Low risk n=251	Massive n=143	Non-massive n=228				
Dilatation of the RV > 3cm, %	71	56.8	82.7	6	63	10.2	0.39	0.5	<0.01	0.11
RV size, cm	3.02±0.68	3.03±0.53	3.07±0.48	2.56±0.44	2.92±0.38	2.51±0.48	0.42	0.87	0.81	0.94
RV hypokinesia, %	9.7	8.1	3.8	0	7	0	0.79	0.62	0.39	0.99
Dilatation of the right atrium > 65 mL, %	61.3	54	57.7	17.9	46	24.7	0.71	0.39	0.15	0.07
Pulmonary hypertension > 30 mm Hg, %	93.5	100	96.2	68.1	100	65.8	0.22	0.99	0.3	0.59
Average pressure in pulmonary artery, %	47.9±13.5	56.2±23.9	54.3±15.3	36.6±15.3	62.6±17.2	34.1±11.9	0.5	0.83	0.71	0.89
Tricuspid regurgitation ≥ 2 degree, %	38.7	56.8	53.4	15.9	42	19.1	0.74	0.11	0.16	0.36
Paradoxical septal movement, %	16	16.2	11.5	0	11.9	0	0.57	0.52	0.94	0.99
Cava vena inferior dilatation > 20mm, %	45.2	18.9	15.4	6	23.8	2.6	0.03	0.51	0.17	0.07

Comment: Comparison of EchoCG criteria of massive PE with the groups of: p₁ – high risk of death; p₂ – moderately high risk of death; p₃ – moderately low risk of death; p₄ – comparison with non-massive PE and low death risk PE.

Right ventricular dysfunction is one of the most important criteria of risk stratification in patients with PE. Commonly it is evaluated using such EchoCG parameters like end-diastolic size of the right ventricle (RV) >3 cm, tricuspid regurgitation > 2 degree, RV hypokinesia, pulmonary hypertension>30 mm Hg, and paradoxical septal motion.

Further we analyzed the prevalence and severity of EchoCG-criteria of PE (Table 1).

The analysis of EchoCG parameters in patients with high, moderately high, and moderately low risk of death assessed with the ESC criteria (2014) and in patients with massive lesions of pulmonary tree and total absence of circulation in 10 and more segmental arteries failed to find significant differences in any of symptoms (p>0.05), apart from vena cava inferior dilatation > 20 mm (p<0.02), that was characteristic for patients with high risk of PE-associated

Table 2. Prevalence of ECG criteria in PE patients

Groups of patients		ECG characteristic		
		S ₁ Q _{III} , %	Negative. T in V ₁ -V ₃ leads, %	RBBB, %
The risk of PE-associated death according to the ESC criteria (2014)	High risk n=31	61.3	48	19.4
	Moderately high n=37	54.1	45.9	24.3
	Moderately low risk n=52	46.2	48.1	31.5
	Low risk n=251	3.2	23.9	21.9
Considering total absence of circulation in segmental arteries	Massive n=143	46.9	48.3	27.3
	Non-massive n=228	4.4	21.9	22.9
p1		0.14	0.98	0.33
p2		0.11	0.8	0.71
p3		0.93	0.98	0.58
p4		0.49	0.6	0.79

TComment: Comparison of ECG characteristics of massive PE with the groups of: p1 – high risk of death; p2 – moderately high risk of death; p3 – moderately low risk of death; p4 – comparison with non-massive PE and low death risk PE.

death. Although it is an indirect sign for evaluation of RV dysfunction, it demonstrates significantly that patients with high risk of death have more pronounced overload of the right heart.

Patients with a low risk of PE-associated death according to the ESC criteria (2014) and patients with non-massive pulmonary arterial tree lesions with absent circulation in less than 10 segmental arteries had no significant differences. All EchoCG criteria of the right heart overload were significantly less frequent in both these subgroups comparing with the other groups ($p < 0.02$).

Correlation analysis revealed weak correlation in patients of the groups of high, moderately high, and moderately low risk of PE-associated death with all EchoCG-signs of PE apart from paradoxical septal movement in patients with high and moderately high risk that had significant moderate correlation ($r = 0.58$, $r = 0.52$). Total absence of circulation in 10 and more segmental arteries had moderate correlation with vena cava inferior dilatation ($r = 0.31$) and paradoxical septal movement ($r = 0.38$).

PE ECG-criteria are not used for stratification of the risk of early death in PE patients. Nevertheless, ECG-signs are important for evaluation of the right heart overload that can be expressed as S₁Q_{III} phenomenon (deep waves S₁ and Q_{III}), T wave inversion in leads III, aVF, V₁-V₃ and complete or partial right bundle branch block (RBBB).

The frequency of the prevalence of the ECG-signs of the right heart overload in PE patients with massive lesions of pulmonary circulation was the following: deep S₁Q_{III} waves – 46.9% of cases, negative T-wave in V₁-V₃ leads – 48.3% of cases, RBBB signs – 27.3% of cases. Comparison of PE subgroups with high, moderately high, and moderately low risk of death according to the ESC criteria (2014) and pa-

tients with massive lesions of pulmonary arterial tree (total absence of circulation in 10 and more segmental arteries) did not reveal any significant differences (Table 2). The same ECG-symptoms of PE except RBBB were significantly less frequent ($p < 0.01$) in the groups of patients with non-massive pulmonary artery lesions and low risk of PE-associated death.

This conclusion is supported by the results of correlation analysis that found weak ($r < 0.3$) correlation between all ECG symptoms of the right heart overload and non-massive PE and low-risk of PE-associated death. High, moderately high, and moderately low risk of PE-associated death and patients with massive pulmonary artery lesions (total absence of circulation in 10 and more segmental arteries) correlated significantly with ECG-criteria of this disease ($r = 0.59$, $r = 0.49$, $r = 0.46$, $r = 0.64$, respectively).

Considering this, we can suggest that registration of ECG symptoms of the right heart overload in PE patients is likely to be related to massive PE. Such ECG signs like S₁Q_{III} phenomenon and negative T wave in V₁-V₃ leads have the highest meaning. RBBB has weaker correlation with massive PE than other ECG signs.

Increased levels of serum troponin is one of the criteria of acute myocardial lesions including RV lesions in PE. We found elevated serum troponin in 58.1% of patients with high risk of death according to the ESC criteria (2014), in 100% cases of moderately high risk, and in 38.5% of patients with massive PE (total absence of circulation in 10 and more pulmonary arteries). In majority of cases these patients were admitted to hospital within 2 days after the disease manifestation. We evaluated the dynamics of this marker concentration depending on time of PE development (Figure 2).

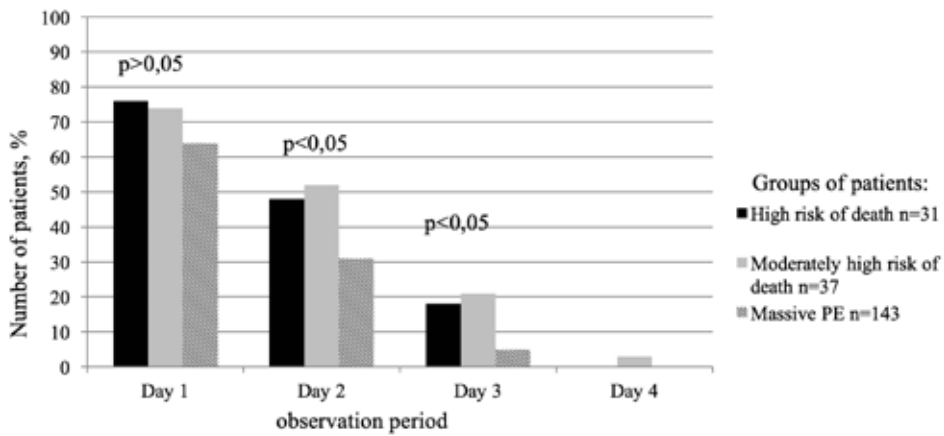


Figure 2. Distribution of elevated troponin levels in PE patients with high and moderately high risk of death and massive PE depending on the duration of the disease

Time of patient’s admission to hospital influenced troponin levels and the frequency of its detection. Considering this, we can assume that a part of PE patients with moderately low risk of early death and admitted to hospital not at the first day could have had elevated serum troponin before and consequently could have been classified as patients with moderately high risk of death, and the treatment strategy of these patients could have been different.

The ESC (2014) recommended to determine the levels of brain natriuretic peptide (NT-Pro-BNP) for evaluation of the presence of RV dysfunction and severity of heart failure. Comparative analysis of aver-

age values of NT-Pro-BNP in patients of the groups of high, moderately high, moderately low, and low risk of PE-associated death demonstrated that the levels of brain natriuretic peptide were significantly lower just in the group of low risk comparing with the other groups (p < 0.01): 2888±515 pmol/L, 2962±421 pmol/L, 3137±652 pmol/L, and 2118±419 pmol/L, respectively. It proves significantly higher right heart overload in PE patients with high, moderately high, and moderately low risk of early death. Similar results were obtained after comparison of PE patients with massive (total absence of circulation in 10 and more segmental arteries) and non-massive lesions (total absence of cir-

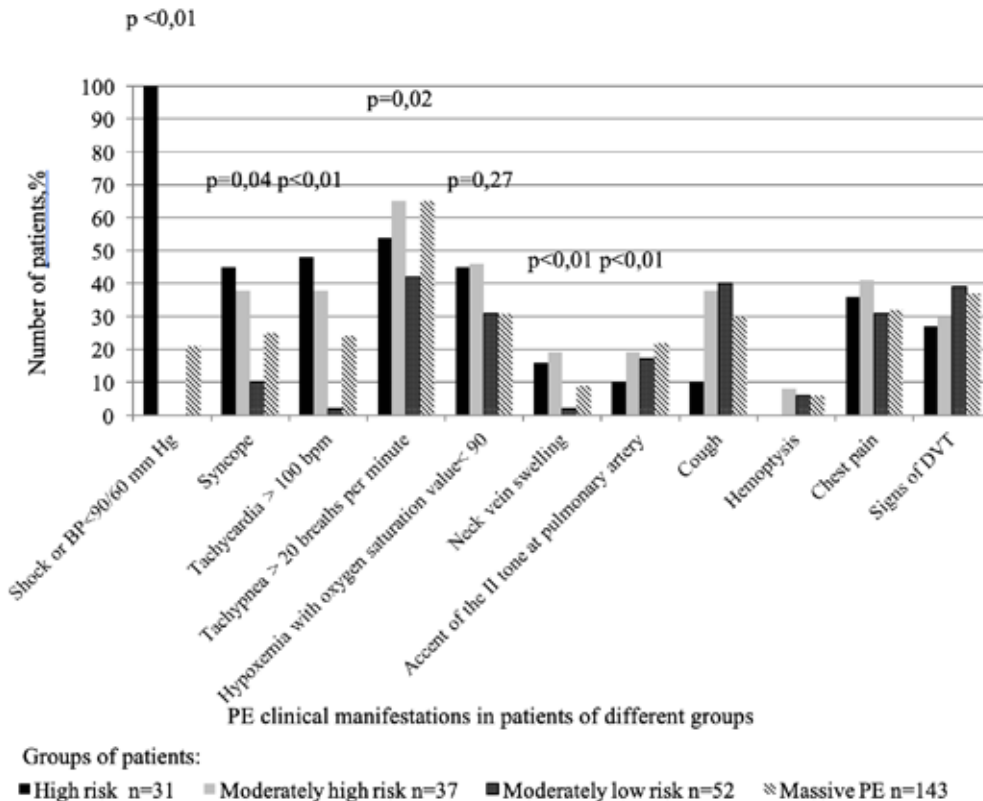


Figure 3. Distribution of symptoms in PE patients with high, moderately high, and moderately low risk of death and massive PE.

circulation in less than 10 segmental arteries) lesions of pulmonary arterial tree: $3\ 857.4 \pm 281.3$ pmol/mL and 1389 ± 664.9 pmol/mL, respectively ($p < 0.01$).

The study of dynamics of brain natriuretic peptide in PE patients in all subgroups demonstrated normalization of its plasma levels by 4-5 days after the manifestation of the disease.

Complaints, anamnesis, identification of risk factors often determine the tactics of examination and treatment of patients with suspected PE. The most characteristic symptoms of PE are: shortness of breath, shock or hypotension with a blood pressure of less than 90/60 mm Hg, collaptoid state, tachycardia with a heart rate of more than 100 beats per minute, chest pain, cough and hemoptysis, cyanosis of the upper half of the body, neck veins swelling and accent of the II tone at pulmonary artery. It is generally accepted that these symptoms have low specificity and do not correlate with the massiveness of pulmonary arterial tree lesions, and their severity is often so insignificant that they remain unnoticed not only by doctors, but also by patients. We found out that patients with low TE-associated risk of death according to the criteria of the ESC (2014) and non-massive lesions (total absence of circulation in less than 10 segmental arteries) of pulmonary arterial tree had the same frequency of symptoms ($p > 0.05$) and they were significantly less frequent ($p < 0.05$) comparing with the patients with massive PE and patients with high, moderately high, and moderately low PE-related risk of death. We performed the comparative analysis of PE clinical symptoms prevalence in these patients (Figure 3).

We found out that many patients with total absence of circulation in 10 and more segmental arteries manifested with such symptoms like accent of the II tone at pulmonary artery and hemoptysis significantly more often than in patients with high risk of PE-associated death ($p < 0.01$), whereas shock or hypotension with systolic blood pressure < 90 mm Hg and pre- or syncopal conditions were less frequent between them comparing with the same group of patients ($p < 0.05$). This is reasonable, since the presence of hypotension or shock in a patient is a selection criterion in this subgroup, which makes it very difficult to assess its significance for comparative analysis. We noted that a considerable part of patients, especially with moderately high risk of early death, that were hospitalized not on the first day of the development of the disease reported episodes of weakness,

dizziness, pre- and syncopal state, which could be caused by hypotension with subsequent stabilization of hemodynamic parameters. Thus, if these patients were admitted to hospital during manifestation of these symptoms, likely they would be assigned to the group of high death risk.

This idea is indirectly confirmed by the absence of a statistically significant difference in presence of pre- or syncopal condition between the groups of high and moderately high risks of PE-associated death ($p = 0.54$). Correlation analysis revealed moderate correlation between high or moderately high risk of death and the presence of pre- or syncopal states in patients ($r = 0.39$ and $r = 0.35$, respectively). Moderate correlation between the volume of lesions and the presence of above-mentioned symptom was found in patients with massive PE ($r = 0.41$). It can be interpreted as another indirect prove of specificity of clinical symptoms in relation to disease duration for stratification of the risk of early death.

Conclusions

The size of pulmonary arterial tree lesions in patients with high, moderately high, and moderately low risk of PE-associated death according to the classification of the ESC (2014) was almost identical.

Elevated troponin and brain natriuretic peptide levels come back to normal values by 3rd and 5th days after the manifestation of the disease that restricts their significance for patients admitted to hospital at later period, since they lower the estimation of death risk and influence the choice of not fully adequate treatment tactics in these patients.

The presence of thrombotic masses in pulmonary arteries that interfere with blood flow in total of 10 out of 20 segmental arteries causes severe hemodynamic disturbances and approaches hemodynamic disturbances of massive PE.

The proposed system of evaluation of the massiveness of pulmonary arterial tree lesions in PE is comparable with the classification of the ESC (2014) from the point of view of prevalence of EchoCG and ECG criteria of this disease and clinical symptoms. Evaluation of massiveness of pulmonary lesions by total absence of distal circulation in 10 and more segmental arteries can complete the stratification of the risk of PE-associated death for determining optimal tactics of patients' management.

Conflict of interest: None declared.

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