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The prediction of adverse outcomes in patients with pulmonary embolism

Pronin A. G., Sivokhina N. Yu., Rakhmatullina A. R., Glukhov D. K.

National Medical and Surgical Center named after N.I. Pirogov of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

Abstract

Objective. *To establish the prognostic criteria of mortality and chronic thromboembolic pulmonary hypertension (CTEPH) in patients with pulmonary embolism (PE).*

Materials and methods. *The study included 155 patients with PE. During the study follow up, 42 patients deceased, 50 patients developed CTEPH 6 months after PE, 63 — complete recanalization of the pulmonary arteries. The course of the disease in these patients was analyzed in order to establish the most significant criteria for adverse outcomes.*

Results. *The symptoms of pulmonary embolism associated with mortality included: cardiac stroke volume reduction according to echocardiography (Echo-CG), the right ventricular to left ventricular diameter ratio over 0.9, blood pressure decrease less than 90/60 mm Hg, a history of syncope, paradoxical interventricular septal motion according to Echo-KG, jugular venous ectasia, SIQIII pattern in the electrocardiogram, over 75 % of thrombotic occlusion of the pulmonary artery according to computed angiopulmonography, concomitant anemia, elevated plasma concentrations of troponin level.*

The probability of CTEPH increased in patients with PE accompanied by: recurrent course of the disease, T-wave inversions in V1 to V3 leads in the electrocardiogram, late therapy initiation, over 60 % pulmonary arterial occlusion, the right ventricular to left ventricular diameter ratio over 0.9, over 30 mm Hg pressure elevation in pulmonary artery.

Conclusion. *Active methods of treatment can be recommended in patients who meet the criteria associated with mortality, including systemic thrombolysis and open or endovascular thrombectomy. Patients with high probability of CTEPH development may require dynamic monitoring followed by the treatment alteration when necessary: anticoagulant therapy correction or the performance of balloon pulmonary angioplasty.*

Keywords: *pulmonary embolism, adverse disease outcome, chronic thromboembolic pulmonary hypertension, mortality.*

AUTHORS

Andrey G. Pronin*, M.D., Ph.D., cardiologist of the Department of Cardiology with Resuscitation and Intensive Care Unit of the National Medical and Surgical Center named after N.I. Pirogov of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

* Corresponding author. Tel.: +7 (977)344-79-44. E-mail: lek32@yandex.ru

Natalya Yu. Sivokhina, M.D., Ph.D., physician of Functional Diagnostics, the Department of Functional Diagnostics of the National Medical and Surgical Center named after N. I. Pirogov of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.
Albina R. Rakhmatullina, M.D., physician of the Department of Cardiology with Resuscitation and Intensive Care Unit of the National Medical and Surgical Center named after N. I. Pirogov of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.
Daniil K. Glukhov, M.D., physician of the Department of Cardiology with Resuscitation and Intensive Care Unit of the National Medical and Surgical Center named after N. I. Pirogov of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.

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Introduction
Pulmonary embolism (PE) is an acute occlusion of pulmonary arteries by thrombi that are developed in the systemic circulation veins [1, 2]. The larger is the diameter and the number of occluded arteries, the greater is the risk of mortality or chronic thromboembolic pulmonary hypertension (CTEPH) development [3–5].

PE mortality ranges from 5 to 24 per 100.000 patients per year worldwide [6, 7]. In most cases, those patients who survived PE, present the reduction of the thrombi with complete hemodynamic parameters recovery. However, in 3–15 % of patients who experienced PE, thrombus organization cause the development of CTEPH, which leads to death in 10–15 % of patients in the following 3–5 years [8, 9].

Modern medicine relies on the establishment of certain risk factors in order to reduce the frequency of complications [10, 11]. Generally accepted, prognostically significant risk factors of early PE-related mortality (30 days after acute episode) include: the presence or absence of hemodynamic stability, elevated plasma troponin level, right ventricular volume overload according to echocardiography (Echo-CG) [12, 13]. The following risk factors are associated with high risk of CTEPH development: severe damage of the pulmonary vascular bed, recurrent PE, the ineffectiveness of ongoing anticoagulant therapy, the presence of right ventricular dysfunction at acute stage according to EchoCG, the initiation of treatment more than 2 weeks after PE [14, 15].

Despite the fact that many studies have been preformed recently, the determination of the most significant prognostic factors and the development of optimal management algorithms for the patients with PE is still highly relevant issue of modern medicine [11].

Materials and methods
In current study we retrospectively analyzed the disease course of 155 patients with PE, who were admitted to the hospital from 2010 to 2021, with high and moderate risk of early PE-related mortality according to the criteria of the European Society of Cardiology. Patients were divided into three groups depending on their disease outcome.

Group 1 included 42 deceased patients (fatal PE) — 18 men (42.9 %), 24 women (57.1 %). The age of patients ranged from 34 to 92 years, mean age was 66.5±12.0 years.

Group 2 included 50 patients with CTEPH that was diagnosed 6 months or more after PE — 26 men and 24 women. The age ranged from 23 to 95 years, mean age — 63.3±14.2 years.

Group 3 was the control group that included 63 patients aged from 26 to 88 years with mean age of 57.7±15.3 years — 32 men and 31 women.

Exclusion criteria were:

1. Limited laboratory and instrumental data;

2. Death or discharge of the patient before all required manipulations were performed.

All the patients on day 1 of admission and in dynamics underwent general and biochemical blood profile assessment that included the determination of the following parameters: D-dimer, homocysteine, antithrombin III, protein S, protein C, erythrocytes, hemoglobin, hematocrit, leukocytes, platelets, creatinine, urea, transaminases, bilirubin, fibrinogen, plasma troponin brain natriuretic peptide. Instrumental studies included the assessment of electrocardiogram phenomena (such as SIQIII, negative T waves, right bundle branch block), doppler ultrasonography of the lower extremity vessels with the establishment lesion and the degree of occlusion visualization, as well as the presence of floating thrombus assessment; Echo-CG with the assessment of qualitative and quantitative characteristics of the right ventricular and right atrial dilation, pulmonary hypertension, tricuspid regurgitation, left ventricular ejection fraction; the visualization of the localization and extent of the lesion of the pulmonary vascular bed using CT angiopulmonography.

The management of patients was performed according to the risk stratification by early PE-related mortality criteria of the European Society of Cardiology.

The study is retrospective and therefore does not conflict with the interests of patients.

The prevalence of clinical, laboratory and instrumental disease signs and its comparative analysis was performed using descriptive statistic methods. The odds ratio (OR) was calculated in order to the assess of the probability of PE adverse outcomes. Statistical analysis was carried out using the "Statistica 6.0" software.

Study results

PE developed as inpatient complication in 57.6% of deceased patients. Among them 75% were patients after surgical treatment. Death occurred within 1–7 hours from the onset of an acute PE episode.

All patients from the fatal PE group had thrombotic occlusion of over 50% of the pulmonary arteries, and 22% of patients from group 2 and 27% from group 3 had the occlusion of less than 50%. The frequency of over 75% pulmonary artery occlusion was statistically significantly higher ($p < 0.01$) in patients from fatal PE group: 54.8% versus 26% in CTEPH group and 17.5% in the control group.

Thrombotic occlusion of the pulmonary arteries of over 60% was seen in 56% of patients from group 2, however, it did not differ significantly from the control group ($p = 0.64$). Treatment outcomes of these patients mostly depended on the rate of disease regression and not on the amount of occlusion. Thus, 24% of patients from the PE with CTEPH group had over 50% decrease of occlusion in first 10 days of inpatient treatment, and in the control group this number reached 84.1% ($p<0.01$).

Potentially fatal PE showed more pronounced clinical signs and, therefore, patients seek medical attention at early stages of the disease. 71.4% of patients with fatal PE were admitted on the first day of PE manifestation. In contrast, only 22% and 23.8% of patients from groups 2 and 3 were admitted at the same period of time, respectively ($p<0.01$). 40% of PE patients with CTEPH were admitted more than 2 weeks after the manifestation of the first PE signs, that was comparable with the control group — 36.5% ($p = 0.7$).

It has been established that patients from with CTEPH were more likely to have recurrent PE course compared with patients from the fatal PE group and the controls — 46% versus 23.8% and 1.6%, respectively ($p<0.01$ and $p<0.01$).

The comparative analysis of clinical data has established that patients from the fatal PE group showed significantly higher frequency of pre- and syncopal states and jugular vein distention compared with the control group. Group with CTEPH did not differ significantly from the controls by the prevalence of these parameters (Table 1).

The analysis of laboratory data between study groups, has found that patients from the fatal PE group had significantly higher prevalence of elevated troponin level and anemia compared with other groups, and patients from the PE with CTEPH group had higher prevalence of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) elevation (Fig. 1).

We have also found that quantitative characteristics of laboratory parameters significantly deviated from the reference values in patients with fatal PE. Mean value of NT-ProBNP in this group was 4665.9±4272.1 pg/ml that is statistically significantly higher than in the control group, 2785.8±3337.4 pg/ml ($p<0.01$), and the mean hemoglobin level in these

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Table 1. **The characteristics of clinical signs in PE patients with various outcomes**

Clinical sign	Study group		p	Study group		p
	Fatal PE n=42	Controls n=63		PE with n=50	Controls n=63	
Systolic BP	114.1±27.3 MMHG	120.7±22.4 MMHG	0.18	128.5±21.5 MMHG	120.7±22.4 MMHG	0.08
Syncope/pre-syncope	57.1%	20.6%	<0.01	20%	20.6%	0.94
Chest pain	23.8%	33.3%	0.3	38%	33.3%	0.6
Cough	4.7%	20.6%	0.02	24%	20.6%	0.67
Dyspnea	85.7%	79.4%	0.41	84%	79.4%	0.53
Hemoptysis	0%	1.6%	0.41	4%	1.6%	0.43
Cyanosis	9.5%	17.5%	0.25	18%	17.5%	0.95
Jugular vein distention	23.8%	3.2%	<0.01	4%	3.2%	0.82
Respiratory rate > 20 per minute	42.9%	30.2%	0.19	42%	30.2%	0.19
Saturation < 90%	23.8%	29.5%	0.52	20%	29.5%	0.25
Heart rate >100 beats per minute	19%	33.3%	0.11	2%	33.3%	<0.01
Accentuated pulmonary component of second heart sound	14.3%	4.8%	0.09	10%	4.8%	0.29
Liver enlargement	14.3%	4.8%	0.09	8%	4.8%	0.52

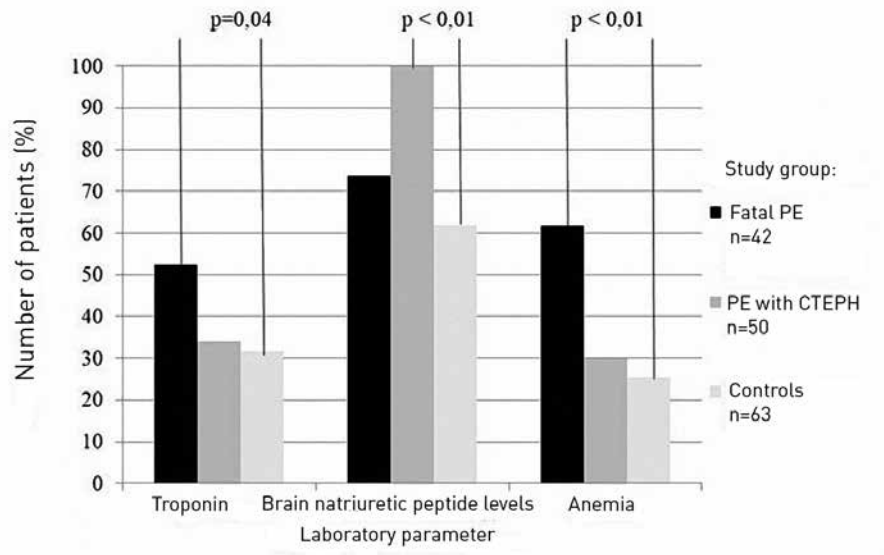

Figure 1. The prevalence of elevated plasma troponin level, brain natriuretic peptide level and anemia in PE patients with various outcomes

groups was 110.1+27.3 g/l and 132.7+20.7 g/l, respectively (p<0.01).

Patients with CTEPH did not differ significantly from the control group by the level of NT-proBNP — 3738±4754.7 vs. 2785.8±3337.4, respectively (p=0.21).

The analysis of the ECG results has established that deep S waves in lead I and Q wave in lead III were significantly more frequent in patients from the fatal PE group, and negative T waves in leads V1-V3 — in patients with CTEPH compared with the control group. (p<0.01) (Fig. 2).

The following Echo-CG parameters were statistically more prevalent in fatal PE group compared with the control group that indicate right heart chambers overload: right ventricle to left ventricle diameter ratio> 0.9, paradoxical movement of interventricular septum and reduced stroke volume, and in patients with CTEPH — right ventricle to left ventricle diameter ratio > 0.9, increased pulmonary artery pressure. It had also been established that death and CTEPH were statistically significantly more often recorded in patients with pulmonary ar-

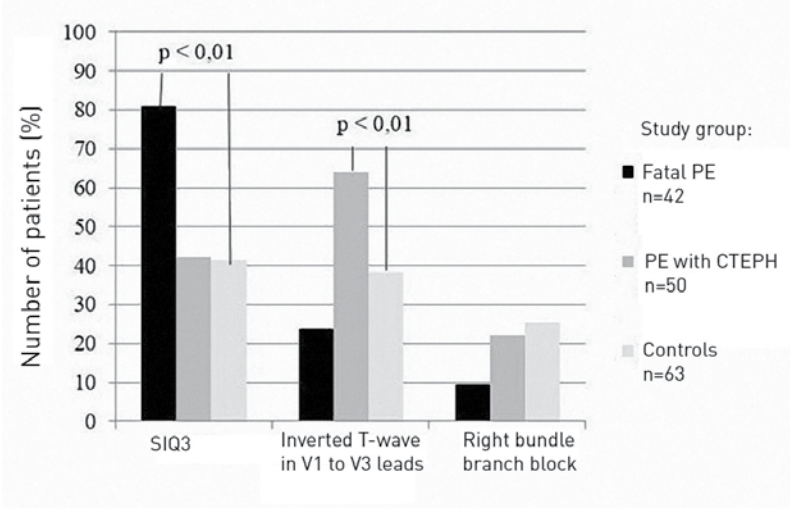

Figure 2. The analysis of ECG phenomena in PE patients with various outcomes

Table 2. **The features of ECG phenomena in PE patients with various outcomes**

Parameter	Study group		p	Study group		p
	Fatal PE n=42	Controls n=63		PE with CTEPH n=50	Controls n=63	
Right ventricle size (four chamber view)	4.4±1.1 cm	4.4±0.6 cm	0.99	4.35±0.64 cm	4.4±0.6 cm	0.67
Right ventricle–to–left ventricle diameter ratio> 0.9	61.8%	26.9%	< 0.01	38%	20.6%	0.04
Systolic pressure in pulmonary artery, mmHg	54.3±19.5	54.8±15.9	0.89	61.9±20.7	54.8±15.9	0.04
Pulmonary artery pressure > 70 mmHg	35.7%	9.5%	0.01	28%	9.5%	0.01
Tricuspid regurgitation ≥ 2 degree	45.2%	39.7%	0.58	54%	39.7%	0.13
Stroke volume	28.1±7 ml	56.7±14.6 ml	< 0.01	58.6±11.3 ml	56.7±14.6 ml	0.45
Inferior vena cava extension > 20 мм	40.5%	23.8%	0.07	28%	23.8%	0.48
Right atrium dilation> 65 ml	40.5%	46%	0.58	62%	46%	0.09
Right ventricular hypokinesis	4.8%	6.3%	0.75	2%	6.3%	0.27
Paradoxical movement of interventricular septum	31%	7.9%	< 0.01	12%	7.9%	0.47

tery systolic pressure over 70 mmHg at acute stage of PE (Table 2).

Thus, fatal outcome of PE is characterized by an acute thrombotic occlusion of over 75% of the pulmonary arteries with the predominance of arterial hypotension over 90/60 mmHg, pre-syncopal and syncopal state, jugular vein distention. The most common laboratory signs in these patients were elevated plasma troponin level and anemia. SIQIII phenomenon has often been registered by ECG in patients with fatal PE, and right ventricle to left ventricle diameter ratio> 0.9, paradoxical movement of interventricular septum, reduced stroke volume — by EchoCG,

The development of CTEPH is facilitated by the recurrent PE with occlusion of over 60% of the pulmonary vascular bed with the following signs of right ventricular overload according to Echo-CG: right ventricle to left ventricle diameter ratio> 0.9, increased pulmonary artery pressure (over 30 mmHg), as well as inverted T waves in V1-V3 leads according to ECG, and the NT-proBNP elevation.

The likelihood of death and CTEPH development, depending on the presence of estimated signs, was assessed using the OR calculation. The following signs increased the risk of death in descending order: reduced cardiac stroke volume according to EchoCG, right ventricle to left ventricle diameter ratio> 0.9, hypotension < 90/60 mmHg, the presence of pre- and syncopal state, paradoxical movement of interventricular septum, jugular vein distention, the presence of the SIQIII phenomenon according to ECG, occlusion of over 75% of the pulmonary vascular bed according to CT angiopulmonography, anemia, increased plasma troponin level (Table 3).

The following criteria increased the likelihood of CTEPH: recurrent PE course, inverted T waves in V1-V3 leads according to ECG, prolonged time to treatment initiation, occlusion of over 60% of the pulmonary vascular bed, right ventricle to left ventricle di-

Table 3. **The significance of clinical signs, laboratory and instrumental parameters in deceased patients after PE**

Symptom	Parameters		
	p	OR	95% CI
Stroke volume reduction	< 0.01	29.5	7.8–81.1
Right ventricle–to–left ventricle diameter ratio> 0.9	< 0.01	16.4	1.9–46.2
Hypotension < 90/60 mmHg	< 0.01	14	5–44
Syncope/pre-syncope	< 0.01	11.79	4.1–34.5
Paradoxical movement of interventricular septum	< 0.01	11.4	2.9–44.9
Jugular vein distention	< 0.01	11.1	2.3–98.9
SIQIII phenomena	< 0.01	7.1	2.5–19.9
Pulmonary arteries occlusion over > 75%	< 0.01	6.9	2.3–20.9
Anemia	< 0.01	5.7	2.1–16.2
Elevated troponin level	< 0.01	4.5	1.6–12.8

Table 4. **The significance of clinical, anatomical, laboratory and instrumental features of PE in patients with CTEPH**

Symptom	Parameters		
	p	OR	95% CI
Recurrent PE	< 0.01	15.1	1.6–19.9
Inverted T-wave in V1 to V3 leads	< 0.01	6.5	2.7–15.8
Late treatment initiation	< 0.01	3.2	1.2–8.5
Lesion > 60% pulmonary vessels (blood flow absence in 13–15 segmental pulmonary arteries)	0.03	2.8	1.1–9.2
Right ventricle–to–left ventricle diameter ratio > 0.9	< 0.01	2.6	1.1–6.3
Pulmonary artery pressure > 30 mmHg	0.04	2.5	1.2–9.7
NT-proBNP elevation	0.24	0.37	0.1–2.0

ameter ratio > 0.9, increased pulmonary artery pressure over 30 mmHg. Increased plasma concentration of NT-proBNP did not statistically significantly affect the development of CTEPH (Table 4), and the reduction of pulmonary vascular bed lesion of over 50% in the first 10 days of treatment significantly reduced the likelihood of this complication (OR = 8.5; 95% CI 1.2–21.4, p<0.01).

Discussion

Nowadays, the risk stratification proposed by the European Society of Cardiology is widely used to determine the risk of PE-related death. The most significant factors that increase the risk of PE-related death are: systolic blood pressure systolic blood pressure < 90 mmHg or systolic blood pressure drop ⩾ 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis, acute overload of the right heart with dysfunction of the right ventricular myocardium according to Echo-CG and its acute damage confirmed by elevated troponin level [12, 13]. We have confirmed the significance of blood pressure decrease < 90/60 mmHg and troponin level elevation. We also presented detailed EchoCG parameters that are the most significant for fatal outcome prediction in PE patients. The prognostic significance of reduced cardiac stroke volume according to EchoCG has been highlighted by our research and is rarely used today in clinical practice and scarcely mentioned in the literature. It should be emphasized that, according to our data, the presence of hemodynamic instability and EchoCG criteria of right ventricular overload is more prognostically significant for the PE adverse outcomes prediction than increased NT-proBNP level that is still debatable and requires further investigation [2, 13].

Other signs associated with the increase of PE-related death established in our study correspond to previous studies [2, 5, 6, 7, 12].

Unlike the immediate outcomes of acute PE, the long-term consequences of PE receive less attention from researchers. This can be explained by the fact that such unfavorable complication as CTEPH is quite rarely registered. According to our data, CTEPH was present in 32.3% of patients with a high and moderate early PE-related death that is comparable to the literature data [8, 9].

The most significant factors associated with high risk of CTEPH included the recurrent PE, occlusion of over 60% of pulmonary vascular bed, prolongation of treatment initiation for over 12–14 days after the first PE signs, the ineffectiveness of anticoagulant therapy [14, 15]. We have estimated detailed EchoCG criteria for right ventricular overload in acute PE that were associated CTEPH: right ventricle to left ventricle diameter ratio> 0.9, pulmonary artery pressure over 30 mmHg. To our knowledge no similar results were previously reported. The presence of T waves inversion in leads V1–V3 according to ECG was not associated with CTEPH development, and recanalization of over 50% of pulmonary arteries at first 10 days of treatment significantly reduced the risk of this complication.

Conclusion

The established prognostic criteria for PE-related mortality and the development of CTEPH will improve our knowledge and ability to predict the de-

velopment of these complications at an acute stage of PE. The assessment of such parameters at early stage of the disease will help healthcare professionals to chose adequate treatment strategy: systemic thrombolysis or thrombectomy in patients with high mortality risk; proper dynamic monitoring in patients with high risk of CTEPH with the correction of the amount and duration of anticoagulant treatment or pulmonary artery balloon angioplasty initiation if necessary.

Conflict of interest: none declared.

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