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Effectiveness of thrombolytic therapy in patients with severe COVID-19 and pulmonary embolism

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Abstract. Current research provides insufficient data on the use of thrombolytic therapy in the treatment of pulmonary embolism in patients with COVID-19. Existing studies present data on the efficacy of thrombolytic drug therapy for thrombotic complications in severe COVID-19. However, these studies either involve a very small number of observations or remain incomplete. This article aimed to assess systemic thrombolysis's effectiveness in intravenous alteplase administration in this pathology. The medical records of 92 patients were analysed. Patients were divided into four groups depending on the therapy administered. Patients in the first group had complications in the form of pulmonary embolism but did not require thrombolytic therapy. Treatment of patients in the first group consisted of prescribing low-molecular-weight heparin at a therapeutic dose. Patients in the second and third groups had pulmonary embolism in the context of COVID-19 and required thrombolytic therapy. The third group differed from the second in the presence of a thrombus in the right heart. Patients in the fourth group had complications in the form of pulmonary embolism, and required thrombolytic therapy, but did not receive it due to a lack of funds. Patients in the second and third groups were immediately treated with unfractionated heparin and alteplase. Thrombolysis was not performed in the fourth group. Mortality rates were studied according to the assigned group. It was established that the risk of death increased ($p < 0.001$) with increasing levels of D-dimer and decreased with increasing PaO2/FiO2 ($p < 0.001$). In the presence of a thrombus in the right heart chambers, the risk of death increased ($p = 0.002$), OR = 3.97 (95% CI 1.66-9.49). A trend towards reducing death risk with thrombolytic therapy was observed ($p = 0.052$). Data were summarised regarding the increased ($p = 0.009$) risk of death when thrombolytic therapy was delayed. Mortality in the fourth group was 100%. The obtained data indicate the significant effectiveness of thrombolytic therapy in the treatment of this pathology

Keywords: thrombolysis; acute respiratory distress syndrome; alteplase; unfractionated heparin

INTRODUCTION

Pulmonary embolism (PE) is a condition that cannot be successfully treated without therapy aimed at dissolving the thrombus. One of the characteristics of COVID-19 is the development of complications related to coagulation disorders, primarily hypercoagulation. According to Y. Wang *et al.* [1], hypercoagulation in COVID-19 patients may manifest through elevated levels of D-dimer, C-reactive protein, and ferritin, and is associated with increased mortality. The idea of using fibrinolytic agents in this group of patients is not new. Data from the ongoing clinical trial of Fibrinolytic therapy to treat ARDS in the setting of COVID-19 infection [2] suggest that fibrinolytic therapy in severe COVID-19 patients improves alveolar ventilation and reduces respiratory failure. This was a phase one clinical trial, where fibrinolytic therapy led to reduced mortality and improved oxygenation. According to the clinical study Tenecteplase in patients with COVID-19, the thrombolytic agent tenecteplase may improve outcomes in patients with severe COVID-19 [3]. The ongoing study Low-Dose Tenecteplase in COVID-19 Diagnosed with Pulmonary Embolism [4] continues to explore the role of this thrombolytic agent in severe COVID-19 cases. According to T. Iba *et*

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al. [5], coronavirus disease causes hypercoagulation with local thrombus formation. Z. Varga *et al.* [6] pointed to endothelial dysfunction and endothelitis as the cause of thromboembolic complications in patients with severe COVID-19. Theoretically, thrombolytics should be used in the treatment of such conditions.

J. Wang *et al.* [7] suggest that thrombolytic therapy may improve survival in critically ill COVID-19 patients. The authors describe their experience treating only three patients. All patients showed improvement after treatment with tissue plasminogen activator. All three patients noted a temporary improvement in respiratory status, and one patient had a sustained improvement. C.D. Barrett *et al.* [8] present the results of treating five COVID-19 patients with alteplase. All patients exhibited respiratory and clinical improvement. The authors concluded that further studies are necessary to determine the optimal regimen for thrombolytic therapy. The ongoing randomised trial by H.B. Moore *et al*. [9] provides data on the efficacy, safety, and dosage of alteplase in the COVID-19 patient population. H.D. Poor *et al.* [10] describe their experience with alteplase in the treatment of four patients with severe respiratory failure caused by severe COVID-19. They suggest that respiratory failure due to pulmonary thrombi in severe COVID-19 requires thrombolysis. According to J.M. Connors *et al.* [11], early thrombolytic therapy in patients with localised pulmonary thrombosis may be considered as a treatment for the uncontrolled coagulation cascade and the interplay between inflammation and coagulation mechanisms in COVID-19.

Thus, existing studies dedicated to investigating the use of thrombolysis in treating pulmonary embolism in severe COVID-19 patients indicate a positive effect of such therapy. However, these studies involve a very small number of clinical cases. All the aforementioned authors insist on the need for further research involving larger patient numbers. This study aimed to evaluate the effectiveness of systemic thrombolysis in providing emergency care to patients with PE against a background of severe COVID-19.

MATERIALS AND METHODS

In this retrospective study, the medical records of 92 patients with severe COVID-19 and PE who were treated in the intensive care unit of Kyiv City Hospital No. 4 from 1 January 2021 to 28 December 2021 (retrospective group) were reviewed. The inclusion criteria were as follows: laboratory-confirmed COVID-19, bilateral pneumonia on computed tomography, partial oxygen pressure in the blood below 60 mmHg when breathing ambient air, a D-dimer level above 0.7 mg/L, and a diagnosis of PE established by ultrasound and computed tomography. All patients underwent ultrasound scanning using the VOLUSON 730 EXPERT and VIVID 7 (GE, USA) systems. The criteria for PE were based on reduced RV output (the "60-60" sign) or reduced contractility of the free RV wall compared to its apex (McConnell's sign). The diagnosis was confirmed using computed tomographic pulmonary angiography when possible, depending on the patient's haemodynamic stability. Computed tomography was performed using a multi-slice Aquilion 64 CT scanner (Toshiba, Japan).

Based on diagnostic results, the patients were divided into two groups. The first group (n = 18) consisted of patients with low-risk and intermediate-low-risk PE, with a Pulmonary Embolism Severity Index (PESI) score ⩽85, corresponding to class I or II, and no signs of RV dysfunction or myocardial injury markers. Treatment for PE involved administering therapeutic doses of low-molecular-weight heparin. The second group (n = 29) included patients with intermediate-high-risk and high-risk PE without the presence of thrombi in the right heart chambers but with signs of RV dysfunction. Criteria for high-risk PE included shock, hypotension, or signs of RV overload (dysfunction), with a PESI score >85, corresponding to class III-V. RV dysfunction was identified by the presence of more than one of the following three signs: RV diastolic diameter (parasternal view) exceeding 30 mm or RV/left ventricular (LV) ratio >1; systolic flattening of the interventricular septum; or an acceleration time of less than 90 ms in the absence of RV hypertrophy. The third group (n = 29) comprised patients with intermediate-high-risk and high-risk PE combined with the presence of thrombi in the right atrium or RV.

The treatment of patients in the second and third groups involved immediate therapy with unfractionated heparin, adjusted based on activated partial thromboplastin time (70-120 seconds), and thrombolysis. Thrombolysis was performed using alteplase. The total dose of alteplase was 100 mg, administered over 2 hours [7]. Thrombolytic therapy was initiated as soon as possible but was most often started after the patient had acquired the necessary medication.

The fourth group (n = 16) consisted of patients with intermediate-high and high-risk PE for whom thrombolysis was indicated but was not performed due to the patient's inability to afford the cost of thrombolytic therapy. Treatment was provided using unfractionated heparin, with the dose adjusted according to the activated partial thromboplastin time (70-120 seconds).

Before initiating therapy, a range of markers characterising the patients' condition were assessed: ferritin levels (by quantitative immunoturbidimetric method) [12], interleukin-6 (IL-6) (by electrochemiluminescent immunoassay) [13], and C-reactive protein (CRP) (by solid-phase immunometric analysis) [14]. The levels of D-dimer [15] and procalcitonin (by immunochemical method with electrochemiluminescent detection) [16] were also measured. Additionally, the day of hospital admission following the onset of illness was recorded for all patients.

Based on the analysis of the coefficients from the four-factor model, the risk of mortality index (YR) was calculated using the following formula:

$$YR = -22{,}9 \times X_1 + 22{,}2 \times X_2 - 1{,}22 \times X_3 - 0.88 \times X_4 + 18{,}66, \quad (1)$$

where $X_1 = 1$ if thrombolysis was used and $X_1 = 0$ if thrombolysis was not used; $X_2 = 1$ in case of Overload and $X_2 = 0$ in case of no Overload; X_3 is the level of Leukocytes; X_4 is the value of PaO2/FiO2/10. The test based on the YR index allows for a highly accurate prediction of the risk of death. The sensitivity of the proposed test is 98% (95% CI 89.4%-99.9%), the specificity of the test is 71.4% (95% CI 55.4%-84.3%), +PV = 80.3% (95% CI 71.6%-86.8%), -PV = 96.8% (95% CI 81.0%-99.5%).

The study was approved by the Bioethics Committee of Kyiv City Clinical Hospital No. 4 [Protocol No. 54 dated 22 December 2020]. All research was conducted by the

fundamental provisions of the Council of Europe Convention on Human Rights and Biomedicine, in compliance with the World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects (with amendments) [17], and the Order of the Ministry of Health of Ukraine dated 23 September 2009 No. 690 [18]. As the study was retrospective in design, Ukrainian legislation did not require informed consent for the research.

As the distribution differed from normal according to the Shapiro-Wilk test, the median (Me) and interquartile range (QI-QIII) were calculated to characterise the quantitative indicators. The Mann-Whitney U test was used for comparisons between the two groups. For qualitative indicators, frequencies (%) were calculated, and Fisher's exact test was employed to compare the two groups. To quantitatively assess the degree of influence of factor variables on the risk of mortality, logistic regression modelling and analysis were utilised. The impact of factor variables was evaluated using odds ratios (OR), with 95% confidence intervals (CI) calculated. The analysis was conducted using MedCalc® statistical software version 20014. Two-tailed critical area criteria were applied, with a critical significance level set at $\alpha crit. = 0.05$.

RESULTS

The study was conducted from 1 January 2021 to 28 December 2021. The overall mortality rate in the intensive care unit was 28.6%, which was comparable to rates reported in other intensive care units globally [19]. Table 1 presents the risk of requiring mechanical ventilation and mortality in the studied groups. The highest risk of death and MV was observed in the fourth group of patients, where 100% were on MV and ultimately died. Mortality rates and the need for MV in the other groups differed significantly from those in the fourth group. The third group had the second-highest mortality and MV rates. The lowest risk of death and MV requirement was observed in the first and second groups.

Table 1. Risk of mechanical ventilation requirement and mortality

Indicator	Low-risk PE without thrombolysis (n = 18)	High-risk PE with thrombolysis (n = 29)	High-risk PE with thrombus in right heart, thrombolysis (n = 29)	High-risk PE with thrombus in right heart, no thrombolysis (n = 16)	p-value
Number of MV cases	7 (38.9%)*	15 (51.7%)*	16 (55.2%)*	16 (100%)	0.002
Number of deaths	7 (38.9%)*	11 (37.9%)*	16 (55.2%)*	16 (100%)	<0.001

Notes: comparisons were made using Fisher's exact test with Bonferroni correction; * – significant difference from the fourth group, $p < 0.05$
Source: provided by the author

To identify factors associated with the risk of mortality, logistic regression modelling was employed. Twelve indicators were analysed as risk factors: group assignment based on whether thrombolysis was performed (Group), age, day of thrombus detection (Day of detection), obesity, D-dimer, CRP, white blood cell count (Leukocytes), platelet count (Platelets), PaO2/FiO2 ratio (PaO2/FiO2), ferritin levels (Ferritin), thrombus in the right chamber, and right ventricular overload. Table 2 presents the results of this analysis.

Table 2. Analysis of mortality risk

Factor		Model coefficient, b ± m	Significance of coefficient deviation from 0, p	OR (95% CI)
Group	Thrombolysis No	Reference		
	Thrombolysis Yes	−0.88 ± 0.45	0.052	0.42 (0.17–1.01)
Age, per year		0.057 ± 0.020	**0.004**	**1.06 (1.02–1.10)**
Day of detection, per day		0.081 ± 0.036	**0.027**	**1.08 (1.01–1.16)**
Obesity	No	Reference		
	Yes	0.24 ± 0.48	0.619	–
D-dimer, per μg/mL		0.47 ± 0.13	**<0.001**	**1.60 (1.24–2.08)**
CRP, per 10 mg/L		0.01 ± 0.13	0.931	–
Leukocytes, per 10^9/L		−0.28 ± 0.16	0.132	–
Platelets, per 10^{10}/L		−0.04 ± 0.11	0.687	–
PaO2/FiO2, per 10 mmHg		−0.52 ± 0.12	**<0.001**	**0.59 (0.47–0.74)**
Ferritin, per 1 mg/L		0.74±0.58	0.199	–
Thrombus in the right chamber	No	Reference		
	Yes	1.38 ± 0.45	**0.002**	**3.97 (1.66–9.49)**
Right ventricular overload	No	Reference		
	Yes	0.78 ± 0.54	0.147	–

Notes: post hoc comparisons were conducted using Fisher's exact test
Source: provided by the author

In the univariate analysis, a trend towards a reduced risk of mortality was observed with thrombolytic therapy (p = 0.052) compared to patients who did not undergo thrombolysis. An increased risk of mortality was associated with advancing age (p = 0.004), with an odds ratio (OR) of 1.06 (95% CI 1.02-1.10) for each additional year. The risk of mortality also increased (p < 0.001) with rising D-dimer levels, OR = 1.60 (95% CI 1.24-2.08) per μg/mL. Conversely, for each 10 mmHg increase in PaO2/FiO2, the risk of mortality decreased (p < 0.001), OR = 0.59 (95% CI 0.47-0.74). The presence of a thrombus in the right chamber significantly raised the risk of mortality (p = 0.002), OR = 3.97 (95% CI 1.66-9.49) compared to patients without thrombi. To identify the set of factors associated with mortality risk in all patients (both those who did and did not undergo thrombolysis), independent variables were selected using multivariate logistic regression models. Four key risk factors were identified: Group, Leukocytes, PaO2/FiO2, and Right Ventricular Overload.

The analysis of the coefficients in the four-factor model suggests that in cases of RV overload, only thrombolysis can prevent a fatal outcome. A table can be constructed to illustrate changes in the risk of death depending on the value of the mortality risk index YR (Table 4).

Table 3. Analysis of mortality risk in the four-factor logistic regression model

Factor		Model coefficient, b ±m	Significance of coefficient deviation from 0, p	OR (95% CI)
Group	Thrombolysis No	Reference		
	Thrombolysis Yes	−22.9	**<0.001**	–
Leukocytes, per 10^9/L		−1.22 ± 0.38	**0.002**	**0.29 (0.14–0.63)**
PaO2/FiO2, per 10 mmHg		−0.88 ± 0.21	**<0.001**	**0.41 (0.27–0.63)**
Right ventricular overload	No	Reference		
	Yes	22.4	**<0.001**	–

Notes: the chi-squared test was used for comparison
Source: provided by the author

Table 4. Risk of death based on the mortality risk index YR

Mortality Risk Index YR	Risk of mortality
<=0	3.2%
0--2	50.0%
2--4	83.3%
>4	100.0%

Source: provided by the author

Next, data from only those patients who underwent thrombolysis (previously referred to as the "thrombolysis yes" group) are analysed. Ten risk factors were considered: age, day of thrombus detection (Day of detection), day of thrombolysis (Day of TL), obesity, D-dimer, CRP, leukocyte count (Leukocytes), platelet count (Platelets), respiratory index (PaO2/FiO2), ferritin levels (Ferritin), and presence of a thrombus in the right heart chamber. The results of the mortality risk analysis in univariate models are shown in Table 5.

Table 5. Analysis of mortality risk in univariate models

Factor		Model coefficient, b±m	Significance of coefficient deviation from 0, p	OR (95% CI)
Age, per year		0.042 ± 0.024	0.078	–
Day of detection, per day		0.042 ± 0.043	0.328	–
Day of thrombolysis, per day		0.55 ± 0.21	**0.009**	**1.73 (1.14–2.62)**
Obesity	No	Reference		
	Yes	0.16 ± 0.59	0.792	–
D-dimer, per μg/mL		0.36 ± 0.15	**0.021**	**1.43 (1.06–1.93)**
CRP, per 10 mg/L		−0.21 ± 0.17	0.200	–
Leukocytes, per 10^9/L		−0.56 ± 0.30	0.063	–
Platelets, per 10^{10}/L		−0.05 ± 0.13	0.710	–
PaO2/FiO2, per 10 mmHg		−0.57 ± 0.17	**0.001**	**0.56 (0.41–0.78)**
Ferritin, per 1 mg/L		−0.05 ± 0.69	0.937	–
Thrombus in the right chamber	No	Reference		
	Yes	0.70 ± 0.53	0.190	–

Notes: the chi-squared test was used for comparison
Source: provided by the author

In the univariate analysis, an increase in the risk of fatal outcomes (p = 0.009) was identified when thrombolysis was delayed, with an OR of 1.73 (95% CI 1.14–2.62). The critical threshold for the model was found to be TL_{crit} = 1 day; exceeding this period significantly increases the likelihood of a fatal outcome. Additionally, an elevated risk of mortality (p = 0.021) was observed with rising D-dimer levels, OR = 1.43 (95% CI 1.06–1.93) per μg/mL increase. The model identified a critical threshold for D-dimer of 5,844 ng/mL; surpassing this value predicts a higher probability of a fatal outcome. Conversely, an increase in PaO2/FiO2 levels was associated with a decreased risk of mortality (p = 0.001), OR = 0.56 (95% CI 0.41–0.78) for every 10 mm Hg. The critical threshold for PaO2/FiO2 was 144 mm Hg, and below this value, the model predicts a higher risk of mortality. To identify a set of factors associated with mortality risk, independent variables were selected using multivariate logistic regression models. Two key risk factors were identified: the day of thrombolysis (Day of TL) and the respiratory index (PaO2/FiO2). Table 6 presents the coefficient values for the model.

Table 6. Mortality risk analysis in the two-factor logistic regression model

Factor	Model coefficient, b ± m	Significance of coefficient deviation from 0, p	OR (95% CI)
Day of TL, per day	0.56 ± 0.26	**0.034**	**1.75 (1.04–2.93)**
PaO2/FiO2, per 10 mmHg	−0.55 ± 0.17	**0.001**	**0.58 (0.42–0.80)**

Notes: the chi-squared test was used for comparison
Source: provided by the author

In the multivariate analysis, a delay in thrombolysis was found to increase the risk of mortality (p = 0.034), with an OR of 1.75 (95% CI 1.04-2.93) per day (standardised for the PaO2/FiO2 ratio). An increase in the PaO2/FiO2 ratio was associated with a decrease in the risk of mortality (p = 0.001), OR=0.58 (95% CI 0.42-0.80) per 10 mm Hg (standardised for the Day of TL). When selecting the optimal threshold for predicting mortality (Y_{crit} > 0.3766), the proposed test showed a sensitivity of 88.9%, specificity of 67.7% (95% CI 48.6%-83.3%), +PV = 70.6% (95% CI 58.6%-80.3%), and -PV = 87.5% (95% CI 70.1%-95.4%). Critical thresholds for high mortality risk on specific days of thrombolysis, depending on the PaO2/FiO2 level, are presented in Table 7.

Table 7. Critical thresholds for high mortality risk based on PaO2/FiO2 levels by thrombolysis day

Day of thrombolysis	PaO2/FiO2 level indicative of mortality
Day 0	<132
Day 1	132-141
Day 2	142-152
Day 3	153-162
Day 4	⩾163

Source: provided by the author

Mortality rates among patient groups were influenced by the severity of PE risk and the treatment administered. Mortality rates in groups two and three showed almost no significant difference. Although the risk of death in the first group was lower, the use of thrombolysis in the second group offset this difference. Thrombi in one of the right chambers of the heart, combined with PE, were found in 489% of PE patients (45 patients), which is 2.7 times higher than the prevalence of right heart thrombi in non-COVID-related PE cases [13]. This is likely attributable to the presence of COVID-19. The presence of a thrombus in one of the right heart chambers worsened the prognosis, with mortality increasing by 1.46 times compared to patients without thrombi. Thrombolysis in patients with high-risk PE and a thrombus in the right heart chamber reduced mortality by 1.81 times.

In evaluating the overall results, it should be noted that the factors associated with a higher risk of mortality in patients were delays in thrombolysis, advanced age, elevated blood D-dimer levels above 5,844 ng/mL, a decrease in the PaO2/FiO2 index below 144 mmHg, and the presence of a thrombus in the right heart chambers. The factor that significantly reduced the risk of death across all study groups was the administration of thrombolytic therapy.

DISCUSSION

The role of coagulation disorders in the pathogenesis of COVID-19 is unequivocal. COVID-19 is a pronounced prothrombotic state [20]. The “cytokine storm” that occurs during the development of COVID-19 activates the coagulation cascade, leading to thrombosis. According to N. Tang *et al.* [21], widespread thrombus deposition disrupts blood supply, often leading to death. T. Iba *et al.* [22] reported that 71.4% of patients who died from COVID-19 were diagnosed with COVID-19-associated coagulopathy. H. Asakura *et al.* [23] suggest that PE is one of the complications of coagulopathy. M.B. Malas *et al.* [20] wrote that impaired coagulation, endothelial dysfunction, dehydration, and limited mobility contribute to a significantly increased risk of PE in COVID-19.

According to B. Mestre-Gómez *et al.* [24], mortality from COVID-19 is directly correlated with blood D-dimer levels. Studies of D-dimer in the examined patients showed a high prognostic value of the indicator, but low specificity of the test for diagnosing PE. According to S.C. Liao *et al.* [25], an increase in D-dimer levels above 700 ng/mL can

be characteristic of both PE and inflammatory syndrome. A decrease in D-dimer levels below 700 ng/mL unequivocally indicates that the patient does not have PE. According to F. De Cobelli *et al*. [26], blood D-dimer levels can increase up to 10,006 ng/mL in case of pulmonary embolism. According to P.K. Woodard [27], an increase in D-dimer above 5,000 ng/mL is a predictor of PE. According to the obtained data, the average D-dimer level in patients with COVID-19 and PE was 5,703.7 ng/mL.

According to M.B. Malas *et al.* [20], patients with hypercoagulability on the background of COVID-19 are at risk of new embolism. PE is accompanied by acute, but potentially reversible, right ventricular failure. Diagnosing PE is challenging due to its nonspecific clinical presentation. Early diagnosis is crucial as immediate treatment is highly effective. In cases of massive PE, urgent restoration of blood flow through thrombosed pulmonary arteries (PAs) is necessary, as suggested by S.V. Konstantinides *et al.* [28].

D.M. Dudzinski *et al.* [29] argue that there are two forms of PE, defined as central (main PA branch) and peripheral (segmental or subsegmental PA branch). According to D. Akdis *et al.* [30], in 4-19% of cases, thrombi in the right heart chambers can lead to PE.

S S.V. Konstantinides *et al.* [28] and D. Akdis *et al.* [30], who studied pulmonary vessel thromboses in the context of COVID-19, raised the question of whether pulmonary vessel thrombosis is a manifestation of recurrent thromboembolism resulting from the extension of primary thrombosis in the inferior vena cava system, or whether it is a primary local thrombosis due to endothelial injury. In other words, the question is where the thrombi form: in the inferior vena cava system, from where they then travel with the blood flow to the lungs, or in the pulmonary vessels themselves. There is pathogenetic evidence to support both theories.

The primary cause of hypercoagulation in COVID-19 is hypoxia. In hypoxic epithelial cells, a factor is produced, the activation of which stimulates the coagulation cascade and leads to the formation of microthrombi [31]. According to F. De Cobelli *et al*. [26], in addition to a possible direct cytopathic effect, the virus can induce a local cytokine-dependent inflammatory response. Viral replication causes cell infiltration, leading to the initiation of coagulation cascades, apoptosis of endothelial cells, and thrombosis of pulmonary vessels, as suggested by J. Helms *et al.* [32].

B. Mestre-Gómez *et al.* [24] reported that direct viral infection of endothelial cells develops in kidney and small intestine tissue. That is, primary thrombi in COVID-19 can form in peripheral vessels, from which they then travel with the blood flow to the lungs. According to the authors of this study, both theories regarding the presumed sites of thrombus formation are correct, i.e., thrombi form both in the inferior vena cava system and directly in the pulmonary vessels. Thrombi in one of the right heart chambers, detected by the study authors, either entered the heart from the inferior vena cava system or formed directly in the heart. They were not related to the pulmonary vessels.

The authors of the study found the prevalence of PE to be an interesting and variable aspect. As noted by E. Martínez Chamorro *et al.* [33], the reported incidence of PE in such patients varies from 0.7% to 57%. In a study by J. Poissy *et al.* [34], 20.6% of cases of PE were reported among 107 patients with severe COVID-19. According to E. Martínez Chamorro *et al.* [33], a multivariable meta-analysis showed a higher incidence of PE in patients with greater disease severity ($P < 0.001$). P. Kapała *et al.* [35] reported that the proportion of patients with acute PE was 23% in a subgroup of 100 patients with severe COVID-19. Simultaneously, pulmonary embolisms were detected in 78.6% of those with severe COVID-19. Y.J. Suh *et al.* [36] reported a prevalence of PE in COVID-19 patients of 16.5%. When several study characteristics were adjusted, the incidence of PE in patients who were critically ill and hospitalised in the intensive care unit was higher at 24.7%, compared to patients who were not admitted to the intensive care unit (10.5%) ($P < 0.001$). In 60.4% of patients, $P = 0.003$, the PE was peripheral. According to the authors, PE was observed in 25.3% of patients with severe COVID-19.

J. Helms *et al.* [32] and J. Poissy *et al.* [34] note that the incidence of PE is higher in patients with COVID-19 pneumonia compared to those with non-COVID-19 viral pneumonia. In the study by E. Martínez Chamorro *et al.* [33], the incidence of PE was analysed in 342 patients with severe COVID-19 and pneumonia and 147 patients with viral cases of pneumonia of other etiologies. Among patients with COVID-19, PE was diagnosed in 26% of patients, compared to 16.3% of patients without COVID-19, p=0.0197; relative risk =1.6. An increased incidence of PE is most often observed in patients with COVID-19 compared to other coronaviruses, according to W. Miesbach *et al.* [37]. The reason for this difference is the cytokine storm. According to N. Mackman *et al.* [38], SARS-CoV-2 causes similar endothelial damage.

Given the increased hepatic production of plasma fibrinogen and pulmonary epithelial fibrinogen in patients with ARDS, there have been suggestions for the use of thrombolytic therapy. The treatment of PE requires risk stratification. C. Basman *et al.* [39] write that for high-risk PE, systemic thrombolysis or embolectomy is advisable, while for low-risk PE, only anticoagulant therapy is chosen. According to P. Kapała *et al.* [35], patients with PE and normal blood pressure, but with signs of right ventricular dysfunction, form an intermediate-risk group, regarding which there are discrepancies regarding the therapeutic strategy. Approximately 10% of such patients may experience haemodynamic decompensation. Systemic thrombolysis should be considered an important treatment method, but the risks of major and intracranial bleeding compete with the overall harm from PE [40]. Numerous hybrid pharmaco-mechanical approaches have been developed to explore the advantages of thrombolysis, but the overall clinical experience with such interventional strategies is limited. Large emboli can rapidly increase pulmonary vascular resistance to a level of afterload that the RV cannot cope with. In such cases, sudden death, usually in the form of electromechanical dissociation, most often occurs. D. Barrios *et al.* [41] believe that right ventricular thrombosis increases the frequency of PE. The formation of a mobile thrombus in the right chambers of the heart, as a cause of PE, is often overlooked. A thrombus formed in the right atrial appendage is a particularly underestimated cause of PE. Right ventricular thrombi can be fixed to the heart structures. Due to the high mortality rate, such a clinical situation is a problem that requires immediate diagnosis

and treatment. Given the existing treatment options for intracardiac thrombi, the optimal therapy remains undefined, according to S. Shi *et al.* [42].

In PE not associated with COVID-19, the incidence of right ventricular thrombosis is 7-18% and is associated with a high probability of early death [30]. The primary treatment methods are thrombolysis and anticoagulants, surgical embolectomy or the use of interventional percutaneous methods, as written by M. Vlachou *et al.* [43]. The advantages of each approach vary depending on the patient's clinical condition. According to A. Anthi *et al*. [44], in the presence of an intracardiac thrombus, anticoagulant drugs can be used alone as first-line therapy. The use of anticoagulants as first-line therapy is proposed in stable patients, especially in the presence of a high bleeding risk. Even though the aforementioned drugs have not been shown to have a direct thrombolytic effect, examples of thrombus dissolution are presented in the literature. M. Vlachou *et al.* [43] believe that thrombus lysis occurs as a result of an indirect effect due to the activation of endogenous fibrinolysis.

In a study by L.M. Burgos *et al.* [45], the treatment of 207 patients with right heart chamber thrombi was analysed. PE was observed in 85% of cases. Overall mortality was 21.3%. Mortality observed after the use of anticoagulants exceeded that after surgical treatment. According to M.P. Rai *et al.* [46], there are several contraindications and limitations to anticoagulant therapy, and its effectiveness is low. The classic surgical method for solving the problem is embolectomy under cardiopulmonary bypass. Surgical treatment has several disadvantages: it is not available in all medical centres, carries the risk of delaying care for several hours, and is associated with a high level of mortality, as noted by J. Keeton *et al.* [47]. New minimally invasive methods include endovascular mechanical thrombectomy with fragmentation; and endovascular thrombus aspiration. These methods are promising, but their use is limited by availability and insufficient compelling evidence, as stated by F. Rajput *et al.* [48].

An alternative to the methods mentioned above could be thrombolysis. The advantages of using systemic thrombolysis include its availability, rapid initiation, and simplicity of the method [41]. However, thrombolytic therapy is not without risk: it can lead to the dislocation of the thrombus or its fragments and their migration to the pulmonary arteries. Although right ventricular thrombosis is considered a predictor of poor prognosis in PE, there is evidence to suggest that such thrombi are transient and should be considered as confirmation of PE. The prognosis in this case is related to haemodynamic status.

The author of the article did not find any studies describing the statistics of right ventricular thrombosis in COVID-19 patients. In the study of A. Anthi *et al*. [44] such cases are described, but without providing statistical data. Thus, at present, there are no established principles for the treatment of PE in COVID-19. Existing studies by A. Alharthy *et al.* [49] and L.C. Price *et al.* [50] described isolated successful cases of the use of thrombolytic therapy. The authors believed that thrombolysis could have a decisive therapeutic value; however, they emphasised that the risk of potential bleeding cannot be underestimated. Currently, a large randomised trial on the use of alteplase in patients with PE in the context of COVID-19, TRISTARDS [40], is underway. The study is currently in its third phase. The author of this article considers it significant that the risk of mortality increases with delays in the initiation of thrombolysis. A multifactorial analysis revealed an increase ($p = 0.034$) in the risk of death associated with deferred thrombolysis, with an OR of 1.75 (95% CI 1.04–2.93) for each day of delay (standardised for the level of PaO2/FiO2). The findings of this study suggest that thrombolysis should be administered as promptly as possible after a relevant diagnosis is established, provided that there are indications for its use. These findings align with recommendations for administering thrombolysis in patients with ischaemic stroke. Thus, the data obtained indicate a notably high prevalence of PE in patients with COVID-19 (25.3%) and a significant efficacy of thrombolysis in treating this complication.

CONCLUSIONS

The primary aim of this study was to evaluate the effectiveness of treatment for PE in the context of severe COVID-19. This objective was achieved through a meticulously designed methodology and thorough analysis of the collected data. The results indicate a high efficacy of systemic thrombolysis in the emergency treatment of patients with PE associated with severe COVID-19. The overall mortality rate in the intensive care unit was 28.6%, which aligns with global statistics. The highest risk of mortality and the need for mechanical ventilation were observed in patients classified in the fourth group. It was established that with each day of delay in administering thrombolysis, the risk of death increased ($p = 0.034$), with an OR of 1.75 (95% CI 1.04–2.93) for each additional day, even after standardisation for the level of PaO2/FiO2. Consequently, timely administration of thrombolytic therapy significantly improved treatment outcomes. A trend towards a reduction in mortality risk was also observed among patients who received thrombolysis ($p = 0.052$) compared to those who did not. These findings underscore the importance of administering thrombolytic therapy promptly in patients with PE associated with severe COVID-19 to lower mortality rates and enhance clinical outcomes. Thus, it can be concluded that systemic thrombolysis is an effective treatment method for patients with PE in the context of severe COVID-19.

This research has practical significance as it allows clinicians to reduce mortality in patients with PE in the context of severe COVID-19. Factors such as the patient's respiratory status, the timeliness of prescribing thrombolytic therapy, and the state of the coagulation system should be carefully analysed. Decisions on the prescription of thrombolytic therapy should be made as soon as possible. Limitations of the study were attributed to the small number of patients examined and its single-centre design. Future studies on the effectiveness of thrombolytic therapy in the context of COVID-19 and PE, if conducted, may provide a greater understanding of the pathogenetic factors of the disease and the mechanisms of action of the therapy used.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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Ефективність тромболітичної терапії у хворих на COVID-19 важкого перебігу та тромбоемболію легеневої артерії

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Анотація. Дані сучасних досліджень містять недостатньо інформації про використання тромболітичної терапії у лікуванні тромбоемболії легеневої артерії на тлі COVID-19. Наявні дослідження містять дані про ефективність терапії тромболітичними препаратами тромботичних ускладнень COVID-19, важкого перебігу. Проте наявні роботи або стосуються зовсім малої кількості спостережень, або залишаються не закінченими. Метою даної статті було оцінити ефективність системного тромболізису у вигляді довенного введення альтеплази при цій патології. Було проаналізовано дані медичних карт 92 пацієнтів. Пацієнтів ділили на чотири групи в залежності від проведеної терапії. Пацієнти першої групи, мали ускладнення у вигляді промбоемболії легеневої артерії, проте не потребували застосування тромболітичної терапії. Лікування пацієнтів першої групи полягало у призначенні низькомолекулярного гепарину в лікувальній дозі. Пацієнти другої та третьої груп на тлі COVID-19 мали тромбоемболію легеневої артерії та потребували тромболітичної терапії. Відмінністю третьої групи від другої була наявність тромбу у правій половині серця. Пацієнти четвертої групи мали ускладнення у вигляді тромбоемболії легеневої артерії, потребували тромболітичної терапії, проте не отримували останню в зв'язку з відсутністю коштів на лікування. Лікування пацієнтів другої та третьої груп полягало в негайній терапії нефракціонованим гепарином та альтеплазою. В четвертій групі тромболізис не проводився. Було досліджено смертність пацієнтів в залежності від встановленої групи. Було встановлено, що ризик летального випадку збільшувався ($p < 0,001$) при зростанні рівня Д-дімеру та зменшувався при зростанні PaO2/FiO2 ($p < 0,001$). За наявності тромбу у правих відділах серця ризик летального випадку зростав ($p = 0,002$), ВШ = 3,97 (95 % ВІ 1,66–9,49). Виявлено тенденцію до зниження ризику летального випадку при проведенні тромболітичної терапії ($p = 0,052$). Було узагальнено дані щодо зростання ($p = 0,009$) ризику летального випадку при відтермінуванні тромболізісу. Смертність пацієнтів четвертої групи становила 100 %. Отримані дані свідчать про про значну ефективність тромболітичної терапії у лікуванні даної патології

Ключові слова: тромболізис; гострий респіраторний дистрес синдром; альтеплаза; нефракціонований гепарин