Folia Cardiologica 2023
vol. 18, no. 3, pages 108–112
DOI: 10.5603/FC.a2023.0010

ISSN 2353–7752
e-ISSN 2353–7760

Pulmonary embolism: does SARS-CoV-2 infection affect the clinical course and prognosis?

Zatorowość płucna — czy infekcja SARS-CoV-2 wpływa na przebieg kliniczny i rokowanie?

Anna K. Żarek-Starzewska[1], Maciej Andrzej Janiszewski[2], Dominika Klimczak-Tomaniak[1], Iwonna Grzywanowska-Łaniewska[3], Aleksandra Wilk[4], Marek Kuch[1]

[1]Department of Cardiology, Hypertension and Internal Medicine, Medical University of Warsaw, Warszawa, Poland
[2]Department of Heart Failure and Cardiac Rehabilitation, Medical University of Warsaw, Warszawa, Poland
[3]Department of Cardiology, Hypertension and Internal Diseases, Mazovian Brodnowski Hospital, Warszawa, Poland
[4]Department of Sport Cardiology and Non-invasive Cardiac Diagnostics, Medical University of Warsaw, Warszawa, Poland

Lekarz Anna Żarek-Starzewska przygodę z kardiologią rozpoczęła w czasach studenckich, aktywnie działając w Studenckim Kole Naukowym przy Katedrze i Klinice Kardiologii II Wydziału Lekarskiego Warszawskiego Uniwersytetu Medycznego pod kierownictwem prof. dr hab. n. med. Marka Kucha. Obecnie jest studentką Szkoły Doktorskiej WUM, a tematyka jej badań obejmuje między innymi rolę microRNA w patogenezie oraz diagnostyce chorób sercowo-naczyniowych. Prace, których była współautorką, zostały zaprezentowane na konferencjach naukowych, takich jak EuroEcho pod patronatem Europejskiego Towarzystwa Kardiologicznego oraz *Warsaw Medical International Congress*. Do zainteresowań pozamedycznych dr Żarek-Starzewskiej należą architektura wnętrz, moda oraz muzyka rockowa.

Abstract

Introduction. Coronavirus disease 2019 (COVID-19) is a disease associated with an increased risk of thromboembolic complications up to 5 months after infection. The study aimed to assess the effect of active or recent (defined as within the past 3 months) COVID-19 on the clinical course of pulmonary embolism (PE) and patients' survival as compared to patients with pulmonary embolism without a history or active COVID-19.

Material and methods. Eighty-seven patients diagnosed with pulmonary embolism, and hospitalized from March 2020 to July 2021 were qualified for the study. The patients were divided into two groups: 1. COVID (+): patients with an active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by the polymerase chain reaction (PCR) or antigen test in the period no longer than 3 months before the diagnosis of PE (n = 38); 2. COVID (–): patients tested negative for SARS-CoV-2 and without typical history of infection (n = 49).

The following data were analysed: clinical data, results of computed tomography, transthoracic echocardiography, ultrasound of deep veins of lower limbs, and results of laboratory tests (D-dimer, N-terminal pro-B-type natriuretic peptide, cardiac troponin I, C-reactive protein [CRP]). For statistical analysis, Statistica version 13 was used.

Address for correspondence: Maciej Andrzej Janiszewski MD, PhD, Zakład Niewydolności Serca i Rehabilitacji Kardiologicznej, Warszawski Uniwersytet Medyczny, ul. Kondratowicza 8, 03–242 Warszawa, Poland, e-mail: maciej.janiszewski@wum.edu.pl

Results. Significant differences between the COVID (+) and COVID (–) groups were observed in the incidence of complete respiratory failure in 39.5% and 6.12% of patients respectively, p = 0.001 and higher in-hospital mortality 26.3% *vs.* 4.08%; p = 0.003. The Cox regression did not reveal any factor significantly associated with in-hospital mortality besides the previous diagnosis of neoplasm (hazard ratio 3.23; 95% confidence interval: 0.81; 12.95; p = 0.09).

The COVID (+) group was characterized by significantly higher levels of CRP (9.43/52.50/113.23 [mg/L] *vs.* 6.40/24.70/47.40 [mg/L]; p = 0.04).

Conclusions. Patients with COVID-19 and PE present higher mortality than patients without concurrent or recent SARS-CoV-2 infection. Further studies are warranted to identify specific factors associated with the observed higher mortality in this population.

Key words: pulmonary embolism, COVID-19, in-hospital mortality

Folia Cardiologica 2023; 18, 3: 108–112

Introduction

Coronavirus disease 2019 (COVID-19), caused by an infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [1], besides its pulmonary manifestation, leads to hypercoagulability in many patients, which in turn becomes a significant risk factor for thrombosis, both in the venous and arterial system [2]. A nearly two-year follow-up of patients with COVID-19 infection shows that pulmonary embolism (PE) and deep vein thrombosis belong to the most common thromboembolic complications in patients with COVID-19. Their incidence is estimated at 20 to 30% in patients in a critical condition [3] and is significantly higher than in the general population (8%) [4, 5]. Whether PE increases mortality in COVID-19 patients remains unclear. Due to the high coincidence of SARS-CoV-2 infection and PE and a relatively high probability of thromboembolic complications even 5 months [6] after the COVID-19 infection, it is essential to identify specific risk factors which will enable an early diagnosis and implementation of adequate treatment to improve patient outcomes.

Objectives

The study aimed to assess the effect of active or recent (defined as within the past 3 months) COVID-19 on the clinical course of PE and patients' survival as compared to patients with PE without a history of active COVID-19. In addition, an attempt was made to identify differences between those subgroups.

Material and methods

The initial analysis included 115 consecutive patients diagnosed with pulmonary embolisms hospitalised at the cardiology department and COVID-19 departments of the hospital between March 2020 and July 2021. Twenty-eight subjects were excluded from the further assessment: 7 due to incomplete diagnostic data, 7 due to SARS-CoV-2 infection following the PE, 13 with COVID–19 defined as typical symptoms and positive antibody testing and 1 due to transfer to another hospital.

The classification of PE severity and the risk of early (30-day) mortality was based on the 2019 European Society of Cardiology Guidelines for the diagnosis and management of acute PE [7].

The patients were divided into two groups:

1. COVID (+): with an active SARS-CoV-2 infection confirmed by the polymerase chain reaction (PCR) or antigen test in the period no longer than 3 months before the diagnosis of PE,
2. COVID (–): patients with a negative PCR test for SARS-CoV-2, no typical history of infection and a negative result of antibody measurement for SARS-CoV-2.

The analysis included anthropometric, clinical, radiologic and laboratory data. The start of COVID-19 was defined as the date of positive PCR or antigen test.

The statistical analysis was performed with the use of the Statistica software, v13. The data were presented as mean (± standard deviation) in case of normally distributed variables, median (1^{st} quartile, 3^{rd} quartile) in case of non-normal distribution and count (percentages) in case of categorical variables. The Pearson χ^2 test was used for nominal variables, the Student's t-test was used for normally distributed quantitative variables and the U-Mann-Whitney test for non-normally distributed quantitative variables. Univariable Cox regression analysis was applied to determine predictive factors of in-hospital mortality.

Results

The final analysis included 87 subjects (50 men), including 38 COVID (+) patients. The mean age was 66.6 years (28–98 years). Active infection with SARS-CoV-2 was confirmed

Table 1. Comparison of clinical course, mortality, hospitalization time and biochemical parameters between COVID (+) and COVID (–) groups

Variable	COVID + group (n = 38)	COVID – group (n = 49)	p
In-hospital all-cause mortality [subjects]	10 (26.3%)	2 (4.08%)	0.003
Respiratory failure during hospitalization [subjects]	15 (39.5%)	3 (6.12%)	0.001
Age older than 65 years [subjects]	0.88/0.94/0.97	0.92/0.96/0.98	0.56
Hospitalization time [days]	6.00/10.50/16.00	3.00/6.00/10.00	0.32
Previous deep vein thrombosis [subjects]	2 (5.26%)	10 (20.4%)	0.04
Concurrent inflammatory process [subjects]	24 (63.2%)	17 (34.7%)	0.008
D-dimer 1 [ng/mL][a]	2077.5/5249.5/34502.50	2020.75/4538.00/9290.75	0.38
D-dimer max [ng/mL][b]	2353.25/5560.00/34502.50	2020.75/4538.00/9290.75	0.40
NT-proBNP 1 [pg/mL][c]	111.50/356.20/1074.50	141.00/509.40/3129.00	0.16
NT-proBNP max [pg/mL][d]	111.50/356.20/1074.50	141.00/509.40/3129.00	0.16
Troponin 1 [ng/L][e]	4.00/15.00/49.50	3.75/19.00/73.00	0.74
Troponin max [ng/L][f]	4.00/16.00/58.00	3.75/21.00/84.75	0.72
CRP [mg/L]	9.43/52.50/113.23	6.40/24.70/47.40	0.04

The data are presented as mean (± standard deviation) in case of normally distributed variables, median (1st quartile, 3rd quartile) in case of non-normal distribution and count (percentages) in case of categorical variables; [a]D-dimer 1 — D-dimer concentration in ng/ml, measured on admission to the hospital; [b]D-dimer max — maximum D-dimer concentration in ng/mL during hospitalization; [c]NT-proBNP 1 — N-terminal pro-B-type natriuretic peptide concentration in pg/mL, measured at hospital admission; [d]NT-proBNP — maximal concentration of N-terminal pro-B-type natriuretic peptide in pg/mL during hospitalization; [e]Troponin 1 — the concentration of high-sensitivity troponin I in ng/L, measured on hospital admission; [f]Troponin max — the maximum concentration of high-sensitivity troponin I in ng/L during hospitalization

in most patients with the PCR test (94.7%, n = 36). The COVID-19 infection had typical clinical symptoms in most patients (97.4%, n = 37), including fever, rhinitis, cough, muscle and joint pain. The median time from the start of COVID-19 to the diagnosis of PE was 8.5 (± 13) days. Twelve patients (13.8%) died during hospitalization. There were no significant differences in anthropometric and baseline clinical parameters, as well as typical risk factors for PE, besides age older than 65 years old in the COVID (+) group, and previous history of deep vein thrombosis, which was more frequent in the COVID (–) group. Neither were any differences observed in the baseline assessment of the PE risk and location and extension of embolic lesions (data not presented).

The clinical course differed significantly between the COVID (+) and COVID (–) groups with a higher incidence of respiratory failure and higher all-cause in-hospital mortality during hospitalisation, which was 5 times higher in the COVID (+) group than in the COVID (–) group (Table 1). However, in the Cox regression analysis, COVID-19 was not a significant predictor of death, which probably results from the limited size of the study group. The only variable significantly associated with mortality was the patient's age. The COVID (+) patients presented significantly higher values of C-reactive protein (CRP) (9.43/52.50/113.23 [mg/L] *vs.* 6.40/24.70/47.40 [mg/L]; p = 0.04). The Cox regression did not reveal any factor significantly associated with in-hospital mortality besides the previous diagnosis of neoplasm (hazard ratio 3.23; 95% confidence interval: 0.81; 12.95; p = 0.09).

Discussion

The results of this study reveal that patients with a diagnosis of pulmonary embolism and active or recent SARS-CoV-2 infection present higher in-hospital mortality than patients without a documented infection. More of them are older and without previous history of deep vein thrombosis, compared to patients without COVID-19.

Currently available literature [8, 9] leaves no doubt that SARS-CoV-2 infection significantly increases the risk of the development of PE and deep vein thrombosis in the lower limbs. Some patients were reported to develop PE even on full-dose anticoagulation [10]. However, the mortality data is not consistent. According to a study supported by the National Institute of Health of the United States, thromboembolic complications in COVID-19 patients contribute to higher mortality in this group [2], while according to other authors, the risk of death estimated based on pooled analyses among patients with COVID-19 and pulmonary embolism is similar [5] to that in patients without a diagnosed pulmonary embolism.

According to scientific reports, male sex and high body mass index are risk factors for pulmonary embolism in patients with COVID; this was not confirmed in this paper. As far as comorbidities are concerned, no specific risk factor

for the development of PE in COVID (+) patients was isolated. This finds confirmation in the available scientific literature [11]. Based on the above data the authors conclude that PE in COVID-19 is to a certain degree [12] affected by SARS-CoV-2 infection as an independent risk factor.

A concurrent inflammatory process (mainly pneumonia) and respiratory failure were observed significantly more often in the COVID-19 group than in the control group. This is correlated with an increased CRP level as well as available scientific reports, which also noticed an increase of other inflammatory parameters (white blood cells, blood platelet, fibrinogen and activated partial thromboplastin time) [12]. A lower saturation in patients with a history of COVID-19, not observed in patients with PE without a concurrent SARS-CoV-2 infection, may result from the lung involvement described in computed tomography.

We did not observe significant differences in D-dimer values between the COVID-19 (+) and COVID-19 (–) patients. However, other studies reported that the values of inflammatory parameters (CRP) and D-dimer in patients with PE and COVID-19 were significantly increased [11], therefore it requires further studies whether the measurement of these parameters may contribute to earlier diagnosis of thromboembolic complications among patients with SARS-CoV-2 or a recent history of such an infection. The consensus of the European Society of Cardiology Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association shows the potential usefulness of serial determination of D-dimers in COVID-19 patients in making decisions regarding diagnostic imaging for thromboembolic complications and potential modification of anticoagulant treatment [13]. Some studies indicate a prognostic value of the concentration of high-sensitivity troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP), but the advisability of their routine determination is still under discussion [13–15] and requires further studies. An increase in the troponin level may result from numerous mechanisms unrelated to myocardial ischaemia including hypoxia, sepsis, systemic inflammation, pulmonary embolism, adrenergic hyperstimulation of the heart during cytokine storm, or myocarditis.

What seems to be clinically significant is the fact that the patients of the COVID-19 group were hospitalised longer, although their course of PE was not much more severe. This leads to a supposition that the SARS-CoV-2 infection is a risk factor for nosocomial complications contributing to prolonged hospitalisation, which may also affect the risk of death of these patients.

One of the main limitations of the study is the exclusion of patients hospitalised in the Intensive Care Unit. Thus, the results should not be extrapolated to the group of patients with severe course requiring hospitalisation at Intensive Care Unit. Typical diagnostics of pulmonary embolism were limited for epidemiological reasons. Not every patient with active SARS-CoV-2 infection received transthoracic echocardiography and ultrasound of the deep venous system. NT-proBNP was not routinely determined in all the patients but was dependent on the clinical situation. The study did not assess the mutated SARS-CoV-2 variants that can affect the clinical presentation of the disease, including, most likely, the incidence of pulmonary embolism.

Patients with COVID-19 and PE present higher mortality than patients without concurrent or recent SARS-CoV-2 infection. Further studies are warranted to identify specific factors associated with the observed higher mortality in this population.

Conflict of interest

None declared.

Streszczenie

Wstęp. Choroba koronawirusowa 2019 (COVID-19) jest związana ze zwiększonym ryzykiem powikłań zakrzepowo-zatorowych do 5 miesięcy po zakażeniu. Celem niniejszej pracy była ocena wpływu czynnego lub przebytego niedawno (w ciągu ostatnich 3 miesięcy) COVID-19 na przebieg kliniczny zatorowości płucnej (PE) i przeżycie pacjentów w porównaniu z pacjentami z zatorowością płucną bez wywiadu lub aktywnej COVID-19.

Materiały i metody. Do badania zakwalifikowano 87 pacjentów z rozpoznaniem PE, hospitalizowanych od marca 2020 do lipca 2021 roku. Pacjentów podzielono na dwie grupy: 1. COVID (+): pacjenci z czynną infekcją SARS-CoV-2 potwierdzoną łańcuchową reakcją polimerazy (PCR) lub testem antygenowym w okresie nie dłuższym niż 3 miesiące przed rozpoznaniem PE, (n = 38); 2. COVID (–): pacjenci z ujemnym wynikiem testu na SARS-CoV-2 i bez typowej historii infekcji (n = 49).

Analizie poddano dane kliniczne, wyniki tomografii komputerowej, echokardiografii przezklatkowej, USG żył głębokich kończyn dolnych, wyniki badań laboratoryjnych (D-dimer, N-końcowy fragment propeptydu natriuretycznego typu B, troponinę sercową I, białko C-reaktywne). Do analizy statystycznej wykorzystano program Statistica w wersji 13.

Wyniki. Zaobserwowano istotne różnice między grupami z COVID (+) i COVID (–) w częstości występowania całkowitej niewydolności oddechowej odpowiednio u 39,5%; 6,12% pacjentów, p = 0,001 i wyższej śmiertelności wewnątrzszpitalnej (26,3% *vs.* 4,08%; p = 0,003). Regresja Coxa nie ujawniła żadnego czynnika istotnie związanego ze śmiertelnością wewnątrzszpitalną poza wcześniejszym rozpoznaniem nowotworu (współczynnik ryzyka 3,23; 95-procentowy przedział ufności: 0,81; 12,95; p = 0,09). Grupa COVID (+) charakteryzowała się istotnie wyższymi stężeniami białka C-reaktywnego (9,43/52,50/113,23 [mg/l] *vs.* 6,40/24,70/47,40 [mg/l]; p = 0,04).

Wnioski. Wśród pacjentów z COVID-19 i PE wykazano wyższą śmiertelność niż u osób bez jednoczesnego lub niedawnego zakażenia SARS-CoV-2. Uzasadnione są dalsze badania w celu zidentyfikowania specyficznych czynników związanych z obserwowaną wyższą śmiertelnością w tej populacji.

Słowa kluczowe: zatorowość płucna, COVID-19, śmiertelność wewnątrzszpitalna

Folia Cardiologica 2023; 18, 3: 108–112

References

1. Akel T, Qaqa F, Abuarqoub A, et al. Pulmonary embolism: A complication of COVID 19 infection. Thromb Res. 2020; 193: 79–82, doi: 10.1016/j.thromres.2020.05.033, indexed in Pubmed: 32526545.
2. Hanff TC, Mohareb AM, Giri J, et al. Thrombosis in COVID-19. Am J Hematol. 2020; 95(12): 1578–1589, doi: 10.1002/ajh.25982, indexed in Pubmed: 32857878.
3. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 75(23): 2950–2973, doi: 10.1016/j.jacc.2020.04.031, indexed in Pubmed: 32311448.
4. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2014; 130(18): 1636–1661, doi: 10.1161/CIR.0000000000000130, indexed in Pubmed: 25246013.
5. Gómez CA, Sun CK, Tsai IT, et al. Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. Sci Rep. 2021; 11(1): 16025, doi: 10.1038/s41598-021-95512-7, indexed in Pubmed: 34362946.
6. Taha M, Nguyen P, Sharma A, et al. Forty-one-year-old man with pulmonary embolism 5 months after COVID-19. Clin Med Insights Circ Respir Pulm Med. 2021; 15: 1179548420986659, doi: 10.1177/1179548420986659, indexed in Pubmed: 33623466.
7. 2019 Guidelines on Acute Pulmonary Embolism (Diagnosis and Management of) ESC Clinical Practice Guidelines.
8. Scudiero F, Silverio A, Di Maio M, et al. Cov-IT Network. Pulmonary embolism in COVID-19 patients: prevalence, predictors and clinical outcome. Thromb Res. 2021; 198: 34–39, doi: 10.1016/j.thromres.2020.11.017, indexed in Pubmed: 33271421.
9. Poyiadji N, Cormier P, Patel PY, et al. Acute pulmonary embolism and COVID-19. Radiology. 2020; 297(3): E335–E338, doi: 10.1148/radiol.2020201955, indexed in Pubmed: 32407256.
10. Gomółka P, Biesiada G, Kąkol J, et al. Pulmonary embolism as a complication of SARS-CoV-2 despite adequate anticoagulation. Pol Arch Intern Med. 2021; 131(5): 471–472, doi: 10.20452/pamw.15901, indexed in Pubmed: 33769002.
11. Soumagne T, Lascarrou JB, Hraiech S, et al. Factors associated with pulmonary embolism among coronavirus disease 2019 acute respiratory distress syndrome: a multicenter study among 375 patients. Crit Care Explor. 2020; 2(7): e0166, doi: 10.1097/CCE.0000000000000166, indexed in Pubmed: 32766562.
12. Cui LY, Cheng WW, Mou ZW, et al. Risk factors for pulmonary embolism in patients with COVID-19: a systemic review and meta-analysis. Int J Infect Dis. 2021; 111: 154–163, doi: 10.1016/j.ijid.2021.08.017, indexed in Pubmed: 34418565.
13. Mueller C, Giannitsis E, Jaffe AS, et al. Cardiovascular biomarkers in patients with COVID-19. Eur Heart J Acute Cardiovasc Care. 2021; 10(3): 310–319, doi: 10.1093/ehjacc/zuab009, indexed in Pubmed: 33655301.
14. Watchmaker JM, Goldman DT, Lee JY, et al. Increased incidence of acute pulmonary embolism in emergency department patients during the COVID-19 pandemic. Acad Emerg Med. 2020; 27(12): 1340–1343, doi: 10.1111/acem.14148, indexed in Pubmed: 33015866.
15. Whyte MB, Barker R, Kelly PA, et al. Pulmonary embolism in hospitalised patients with COVID-19. Thromb Res. 2020; 195: 95–99, doi: 10.1016/j.thromres.2020.07.025, indexed in Pubmed: 32682004.