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PULMONARY EMBOLISM IN COVID-19

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Abstract

COVID-19 pandemic is recognized as a present day major public health burden. Risk factors for developing a more severe course of COVID-19 include increased levels of C-reactive protein and D-dimer. Pulmonary embolism (PE) is challenging in patients with COVID-19. The purpose: to analyze clinical and paraclinical manifestations of PE in patients with COVID-19 in order to develop a system for its early diagnosis, prediction of complications, prevention and treatment. 52 patients aged 28 - 81 y.o. with a diagnosis "Acute respiratory disease COVID-19" have been examined during 2020-2021. (98.08±1.9)% of PE patients had a history of one or more comorbidities, including obesity (80.77%), coronary heart disease (96.15%), hypertension (98.08%), peripheral arteries (92.3%), type 2 diabetes mellitus (48.08%). Evaluation of laboratory parameters revealed increasing lymphocytopenia, leukocytosis, neutrophilia, thrombocytopenia ($p<0.05$). Biochemical parameters showed high CRP, increase in creatinine, decrease in glomerular filtration rate ($p<0.05$). A direct relationship was found between overweight and an increase in the content of C-RP in COVID-19 and PE patients. Conclusions: age over 65, hypertension and obesity are risk factors for severe course of COVID-19 and PE.

Key words: COVID-19; PE; D-dimer; coagulopathy

In December 2019 a new coronavirus - COVID-19 - was detected in Wuhan and quickly spread around the world. In March 2020 the World Health Organization declared a pandemic of a new outbreak of coronavirus [1, 14].

Most people tolerate the disease caused by COVID-19 easily, while 20% develop a severe course with a high mortality rate [2]. Today more than 300 million people (about 4 % of the world's population) is infected with COVID-19 of which 5 million have died (0.65 per 1000 population) [3, 4].

Potential risk factors for the development of a more severe course of COVID-19 are D-dimer increased level, a high score for sequential organ failure, and advanced age [5, 6].

Persistent hemostatic changes in patients with severe or critical COVID-19 [1, 13, 14] is an additional to respiratory manifestations serious problem leading to disability.

A growing number of authors report the development of complications associated with thrombosis in COVID-19 patients, including thrombosis of extracorporeal circuits for continuous venous hemofiltration; thrombosis associated with a central venous catheter; deep vein thrombosis and pulmonary embolism (PE). Most of these complications occurred in patients treated in the intensive care unit, most of them received routine thromboprophylaxis [7, 8].

PE is a life-threatening condition that occurs with a frequency of 50–200 per 100 thousand of population [9, 10], and ranks third in Europe in the structure of cardiovascular mortality, i.e. 300–370 thousand of fatalities annually [10, 11].

Diagnosing PE can be challenging in COVID-19 patients. PE symptoms overlap with those of COVID-19, and the first signs may be missed in a patient who is already short of breath [7]. At the same time, the clinical signs and symptoms of deep vein thrombosis in the intensive care unit patients remain unnoticed, due to the close attention of medical personnel primarily to the respiratory status [12].

Despite a sufficient number of publications on the severe course and possible complications, today there are no generally accepted data on the early diagnosis and effective prevention of PE in patients with COVID-19.

The aim: to analyze the clinical and paraclinical manifestations in patients with COVID-19 and PE in order to develop a system for early diagnosis, prediction of complications, their prevention and treatment.

Materials and methods

The study was conducted on the basis of the Municipal Clinical Infectious Diseases Hospital (Odessa, Ukraine) during 2020-2021. COVID-19 patients aged 28-81 years old. The

group of observation included 52 patients, 16 women (30.77±6.4) and 36 men (69.23±6.4). They all had clinically verified diagnosis of PE.

All the subjects gave informed consent to participate in the examination and processing of their personal data (Order of the Ministry of Health of Ukraine dated January 21, 2016 N 29), as well as in compliance with moral and ethical principles in accordance with the main provisions of the World Medical Association Declaration of Helsinki (1994, 2000, 2008) and the positive decision of the Commission on Bioethics of the Odessa National Medical University.

All patients underwent general clinical, laboratory and instrumental examinations and received treatment in accordance with national protocols (Order of the Ministry of Health of Ukraine No. 762 dated April 2, 2020, No. 1653 dated July 21, 2020, No. 1979 dated September 20, 2021).

The diagnosis of COVID-19 was confirmed by real-time PCR (Abbott, USA) and the detection of IgM and IgG antibodies to SARS-Cov-2 by enzyme immunoassay (Euroimmun, Germany).

In the group under study clinical and instrumental indicators and laboratory characteristics were analyzed at the time of admission to the hospital and during PE development.

Statistical analysis was carried out with computer programs "Microsoft Excel" using parametric and non-parametric methods, indicating the average values and standard error of the mean (M±m). The significance of differences in mean unrelated samples was assessed using Pearson's $\chi 2$ test and Student's t-test.

Results

A retrospective analysis of 1436 medical records was done. According to it the proportion of patients with verified PE in the final diagnosis was equal to 3.62% (n=52). The average age of patients included in the study was 66.87±10.74 y.o.

Almost all of them (98.08±1.9)% had a history of one or more concomitant chronic diseases, such as obesity (80.77%), coronary heart disease (96.15%), hypertension (98. 08%), peripheral arterial disease (92.3%), type 2 diabetes mellitus (48.08%), varicose veins (42.3%), chronic obstructive pulmonary disease (26.92%), oncology (17.3 %) and etc.

The possibility of PE in COVID-19 patients was suspected in the presence of one or more clinical symptoms such as chest pain or syncope ((90.38±4.09)% and (7.69±3.69)%, respectively). Dyspnea was observed in all COVID-19 patients under observation. At the same time, with the development of PE in (48.08±6.93)%, a sharp decrease in saturation was

noted. In 20 (38.46±6.74)% of patients, arterial hypotension and shock developed very quickly.

The scales CHA(2)DS(2)-VASc, Padua and coagulopathy caused by sepsis were used to predict complications. This took into account age, the presence of concomitant diseases, deep vein thrombosis in history, platelet count, prothrombin time, D-dimer, fibrinogen.

The severity of PE was determined by the risk of early mortality (Table 1).

Table 1- Risk of death in patients with PE and COVID-19

Indicator	Group, n=52	Criterion χ^2	P*
Male gender, %	69.23±6.4	1.926	>0.05
Age >65, %	75.0±6.0	23.693	<0.001
Body mass ratio 30%	80.77±5.46	5.184	<0.05
Diabetes mellitus,%	48.08±6.93	0.924	>0.05
Hypertension,%	98.08±1.9	25.490	<0.05
D-dimer, ng/ml, %	94.23±3.23	6.783	<0.05
CRP, mg/l ,%	86.53±4.73	8.132	<0.05
Fibrinogen, g/L, %	30.77±6.4	0.752	>0.05
Leucocytes x 10^9l,%	56.54±6.87	0.650	>0.05
Neutrophils x $\times10^9$/l, %	61.3±6.75	2.294	>0.05

**Value is significant at p<0.05*

When assessing laboratory parameters, it was found that patients with COVID-19 complicated by PE had increasing lymphocytopenia, leukocytosis, and neutrophilia ($p<0.05$). At the same time, the level of hemoglobin and fibrinogen remained unchanged compared to baseline values ($p>0.05$). The ratio of neutrophils to lymphocytes changed critically (from 4.19 to 15.82 units; $p<0.05$).

44 (84.62±5.0)% of patients had thrombocytopenia ((142±7.36)×10^9/l). At the same time, thrombocytosis was detected in 4 (7.69±3.69)% of COVID-19 patients.

Analysis of blood biochemical parameters showed an increase in creatinine and a decrease glomerular filtration rate ($p<0.05$). CRP values (mean 94.2±7.36 mg/l) remained very high throughout the entire observation period ($p<0.05$). In patients with COVID-19 and PE, a direct relationship was found between overweight and an increased value of CRP at the time of hospitalization ($p<0.05$) and during the development of PE ($p<0.01$).

When evaluating coagulation markers, the level of D-dimer was measured every 2-3 days. It was increased in 50 (94.23±3.23)% of patients and amounted to 952 (904.1-1000.2) ng/ml.

Fibrinogen was elevated in 16 (30.77±6.4)% of patients, and averaged 4.2±1.27 g/l. Most of them (13, 81.25%) were over weighted (BMI>25).

A decrease in the prothrombin index (average 73.3±8.12%) was observed in (25.0±6.01)% of patients with PE and COVID-19.

Activated partial thromboplastin time (APTT) in surviving patients with COVID-19 was 27.7 (21.8–44.0) and in deceased patients it was 41.8 (34.1–51.0); $p<0.05$.

Prothrombin time (PT) was increased in 50 (96.15±2.69)% of patients with COVID-19 and PE, and averaged 18.6±7.46 s. ($p<0.05$)

Concomitant diseases significantly increase the risk of a severe course of the disease and an unfavorable outcome: almost 6.9 times in people with obesity ($p<0.01$), 9.0 times in those with diabetes ($p<0.05$), 26 times in hypertensive subjects ($p <0.05$), 12 times under the presence of coronary heart disease ($p <0.05$), 5.0 times under atrial fibrillation ($p <0.01$). Moreover, a direct relationship was found between the presence of excess body weight and severe course disease in patients with COVID-19 and PE ($p<0.05$).

Thus, the risk factors for the development of a severe course of COVID-19 complicated by PE and death include the presence of concomitant diseases (hypertension, coronary artery disease, diabetes mellitus, obesity), a high level of D-dimer, thrombocytopenia, neutrophilia, ($p<0 .05$).

Among COVID-19 and PE patients on the background of obesity, in comparison with obesity-free patients, a higher proportion of people with severe COVID-19 ($\chi 2=5.184$; $p<0.05$) was revealed. Thus, these patients had more low rates of oxygen saturation upon admission to the hospital ($U=46.5$; $p<0.05$) and PE developed significantly more often (40.38%; $p<0.05$).

Thrombosis prophylaxis was carried out from the first day of hospitalization to all in-patient unit subjects. Anticoagulant therapy was administered to all patients in the intensive care unit (enoxaparin, low molecular weight heparins). The dosage depended on body weight. Patients were also prescribed rivaroxoban 15 mg once /day and/or clopidogrel 75 mg, also once /day.

The incidence of PE in COVID-19 patients in the intensive care unit was (17.6%).

When the first signs of thrombotic complications appeared, patients were transferred to therapeutic doses of low molecular weight heparins. Alternatively, fondaparinux sodium 2.5 to 10 mg was used depending on body weight and severity of the condition. A favorable outcome of PE was noted in (9.62±4.17)% of patients with COVID-19.

Conclusions

The data obtained suggest that age over 65, hypertension, and obesity can be considered risk factors for severe course of COVID-19 and PE.

The use of scales for assessing the risk of developing thrombotic complications is a convenient way to assess the nature of hemostasis system disorders in patients with COVID-19, taking into account possible difficulties in conducting additional instrumental examinations.

Timely use of anticoagulants, primarily low molecular weight heparins, is optimal for the prevention of thromboembolic complications in patients at high risk for COVID-19.

The course and prognosis of thromboembolic complications in patients with COVID-19 require further clarification in the prospective follow-up of these patients.

References:

1. DiMinno, A., Ambrosino, P., Calcaterra, I., &DiMinno, M. (2020). COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies. Seminars in thrombosis and hemostasis, 46(7), 763–771. 9

2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72?314 cases from the chinese center for disease control and prevention. JAMA. 2020. [PMID: 32091533] doi:10.1001/jama.2020.2648.

3. World statistics COVID-19. Access mode: https://covid.observer/.ru/ (in Russian)

4. Kharchenko Yu. P., Zaretskaya AV, Buyko OO, Ilyina-Stognienko V. Yu. Features of the clinical and paraclinical course of COVID-19 in children. Herald for Marine Medicine. 2021. - N 2. - P. 8 – 14 (in Ukrainian)

5. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-847. [PMID: 32073213] doi:10.1111/jth.14768.

6. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med. 2020;173(4):268-277. doi:10.7326/M20-2003

7. Middeldorp, S., Coppens, M., van Haaps, T. F., Foppen, M., Vlaar, A. P., Müller, M., Bouman, C., Beenen, L., Kootte, R. S., Heijmans, J., Smits, L. P., Bonta, P. I., & van Es, N. (2020). Incidence of venous thromboembolism in hospitalized patients with COVID-19. Journal of thrombosis and haemostasis : JTH, 18(8), 1995–2002.

8. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.

9. Palm, V., Rengier, F., Rajiah, P., Heussel, C. P., & Partovi, S. (2020). Acute Pulmonary Embolism: Imaging Techniques, Findings, Endovascular Treatment and Differential Diagnoses. Akute Lungenarterienembolie: Bildgebung, Bildbefunde, endovaskuläre Therapie und Differenzialdiagnosen. Ro Fo :Fortschritte auf demGebiete der Rontgenstrahlen und der Nuklearmedizin, 192(1), 38–49. https://doi.org/10.1055/a-0900-4200

10. Raja AS, Greenberg JO, Qaseem A. et al. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015; 163: 701-711

11. Konstantinides SV, Torbicki A, Agnelli G. etal. 2014 ESC guidelines on the diagnosis andm anagement of acute pulmonary embolism. Eur Heart J 2014; 35: 3033-3069, 3069a-3069k

12. Middeldorp S, Coppens M, van Haaps TF, et al. . Incidence of venous thromboembolism in hospitalized patients with COVID-19. Preprints 2020; preprint

13. Wu C, Chen X, Cai Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease - 2019 pneumonia in Wuhan, China JAMA Intern Med2020; Doi: 10.1001/jamainternmed.2020.0994

14. Mo P, Xing Y, Xiao Y. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China Clin Infect Dis2020; Doi: 10.1093/cid/ciaa270

15. World Health Organization Corona virus disease 2019 (COVID-19): Situation Report, 51 2020. Available at:https://apps.who.int/iris/handle/10665/331475. Accessed July 15, 2020