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STATISTICAL ANALYSIS OF PATHOLOGICAL ANATOMY OF THROMBOEMBOLIC COMPLICATIONS IN CORONAVIRUS INFECTION

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ABSTRACT

This article compares the scientific findings of world scientists aimed at elucidating the pathological anatomy of thromboembolic complications in the composition of coronavirus infection and statistical analysis of coronavirus infection in our country. Statistical analysis showed that complications of thromboembolism in the period from 2019 to 2021 as part of coronavirus infection in the world will be 37%, of which 14% will be pulmonary embolism. Thromboembolic complications in patients with coronavirus infection, including sinus thrombosis, are currently considered the most common cause of death from Covid infection.

Key words: pathological anatomy, coronavirus infections, sinus thrombosis, thromboembolism, thrombosis.

INTRODUCTION

Currently, during the pandemic, there are too many death cases due to thrombo-embolic complications of corona virus infection. Prevention and

treatment of thromboembolic complications is an urgent problem. Thromboembolism is an acute blockage (embolism) of a blood vessel with a blood clot that has broken off from its place of origin (heart, vessel wall) and entered the blood circulation. As a result of thromboembolism, blood flow in blood vessels stops, tissue ischemia occurs in the occlusive vascular basin, often leading to an ischemic infarction.

Etiology and pathogenesis: Thromboembolism is the most common type of vascular embolism. Thromboembolism is caused by damage to the endocardium (in endocarditis, myocardial infarction) or vascular endothelium (in aortic aneurysm, aortitis, thrombophlebitis, vasculitis, atherosclerosis, etc.) and formation of thrombosis. Medicines that slow down fibrinolysis and bleeding also increase blood clot formation. Cardiac arrhythmias, especially paroxysmal tachycardia and fibrillation, contribute to the formation and separation of thrombus in the cardiac cavities. The formation of blood clots in the right chambers of the heart, large veins often causes the risk of pulmonary embolism. (4). COVID-19 (2019 new coronavirus disease) continues to threaten the global health system. Epidemiological evidence shows that SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is most susceptible to patients with metabolic and chronic diseases. In patients with severe acute respiratory syndrome associated with movement insufficiency contaminated with coronavirus-19, risk of venous thromboembolism increases when if dehydration occurs during self-isolation. Patients' hospitalization for the treatment of coronavirus disease (COVID-19) greatly increases the risk of developing pneumonia and thromboembolic complications. These thromboembolic events are the result of at least two distinct mechanisms. Pulmonary microvascular thrombosis (immunothrombosis) and hospital-associated venous thromboembolism.

Immunothrombosis – through the course of evolution, the blood coagulation system developed as a result of the immune response, with fibrin preventing the spread of pathogenic microbes into the body. When viruses such as SARS-CoV-2 enter the body, during acute viremia, cytokine production, activation of monocytes and macrophages, interleukin-6 production (IL-6) and potentially the initiation of the coagulation system are induced. The entry of SARS-CoV-2 into human cells is ensured by the effect on angiotensin enzyme-2 (ACE-2) receptors. These receptors are found in many tissues such as pneumocytes, heart, kidney, endothelium, macrophages and intestine. The main part of the cells expressing ACE-2 are alveolar epithelial type II cells of lungs (type-II pneumocytes). The abundance of ACE-2-expressing cells in the alveoli of the lungs and the large surface area of the lungs make it the main target organ for viruses. Extravascular fibrin develops in

the pathogenesis of acute lung injury in COVID-19. Immunothrombotic inflammatory response, combined with hypoxia and increased local tissue factor production develop in patients with SARS-CoV-2 infection. Monocyte activation and subsequent cytokine hyper-production can also lead to endothelial cell activation, which involves a change from an antithrombotic phenotype to a procoagulant phenotype.

Coronavirus disease 2019 (SARS-Cov-2) is a new viral infection causing acute respiratory distress syndrome (ARDS) that was first identified in December 2019 in Wuhan, China. This infectious disease quickly spread to almost all countries, causing the most dangerous pandemic since the Spanish flu of 1918-1920 [1]. One of the worst features of COVID-19 is the risk of thromboembolic complications and a severe coagulopathy called COVID-19-induced coagulopathy (CAC), with a venous thromboembolism (VTE) rate of about 25 percent. Damage to vascular endothelial cells infected with SARS-Cov-2 can lead to neutrophil collection and immune complex formation. Contemporary activation of coagulation, inflammation, and immune pathways is consistent with the concept of immunothrombosis [2]. These two processes are initially triggered by SARS-Cov-2-induced diffuse endothelial dysfunction through angiotensin-converting enzyme (APF-2) and transmembrane protease serine 2 (TMPRSS2) receptors, which are now recognized as specific entry sites of the virus into the vasculature. Rare autooptic studies of patients with COVID-19 show extensive areas of inflammatory infiltration associated with interstitial edema, thrombotic lesions, and changes in alveolar architecture, with characteristic vascular features consisting of severe endothelial damage and disrupt of cell membranes, termed intracellular virus-associated endotheliitis. Histological analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis with microangiopathy, including the formation of hyaline membranes and infiltration of macrophages and monocytes [3,4,5].

Although these results were mainly observed in patients older than 65 years with a history of comorbidities, occasionally, pulmonary complications with extensive parenchymal damage requiring invasive ventilation were also observed in some younger patients. A recent European Society of Cardiology (ESC) article on Atherosclerosis and Vascular Biology focused on endothelial damage as a major target organ for thrombotic complications [6]. This complex scenario involves an altered immune and inflammatory response, oxidative stress, damage to the endothelial structure, and platelet activation. Histological markers are also mediated by both specific populations of lymphocytes associated with increased immunity and by pre-coagulation markers that predispose to intravascular

thrombosis. Thrombotic activity can increase in other vascular areas such as coronary and cerebral vessels, leading to acute coronary syndrome and stroke, respectively [7,8]. Although these common findings have been reported in the recent literature, which patients are at increased risk of developing immune and thromboembolic (TE) complications remains to be determined. Another point that remains to be determined is whether current clinical laboratory and diagnostic approaches applied to patients with COVID-19 are able to rapidly detect and ultimately prevent clinical deterioration. A better understanding of the mechanisms linking infectious diseases to embolic complications is a challenge for future research. Of note, the altered sign of the coagulation cascade and the specific investigation of molecular and protein signaling dysfunction may lead to treatment optimization.

This is a peer-reviewed review of thrombotic complications associated with SARS-Cov-2 infection, including randomized clinical trials, controlled trials, meta-analyses, and position papers published in the field. We excluded clinical cases and single center studies from our paper case reports. Searching terms and definitions for all articles published in Pub Med between December 2020 and March 2021 included taking the terms such as "risk factors," "thrombosis," "coagulation," "vascular complications," and "antithrombotic therapy."

Epidemiological studies have shown that elderly patients with a higher severity of comorbidity are more prone to develop adverse complications after infection with COVID-19. The presence of risk factors such as cardiovascular disease (CVD) or simply diabetes and heart disease in the medical history leads to the end of the disease with unpleasant consequences [9]. Accordingly, admission to the emergency department (ED) and the need for invasive ventilatory support are more common in patients with cardiovascular disease, whose mortality is 5-10 times higher than in patients without risk factors [10, 11]. Patients with a high severity of cardiovascular diseases and comorbidities are more likely to develop cardiac complications, mainly due to increased complications of TE and ARDS [12, 13]. These results were confirmed in 5,700 hospitalized patients in the New York area, showing that cardiovascular risk was independent of race and geographic region [14].

In a meta-analysis of 75,000 subjects, hypertension, cardiovascular disease, diabetes, smoking, chronic obstructive pulmonary disease, malignancy, and chronic kidney disease were the most common underlying medical conditions associated with hospitalization [12]. Of note, another analysis evaluating cardiac biomarkers found elevated levels of troponin (TnT), pro-V-type N-terminal natriuretic peptide (NT-proBNP), and C-reactive protein in patients with CVD. In-

hospital mortality was similarly associated with a history of cardiovascular disease and TnT level: patients without known cardiovascular disease with elevated TnT levels were relatively better, but patients with cardiovascular disease or elevated TnT levels (69 percent) was unacceptably many during hospitalization [13]. Available data suggest that myocardial injury is significantly associated with severe COVID-19 outcomes, and this trend is likely due to the presence of CVD. Studies have shown that TnT levels are significantly correlated with C-reactive protein (CRP) and NT-proBNP levels, providing further evidence linking myocardial injury to the severity of inflammation. Inflammation and the associated cytokine storm can affect the respiratory and cardiovascular systems; otherwise, it can cause myocarditis, cardiac arrhythmias, acute coronary syndrome, pulmonary embolism, and disseminated coagulopathy. Although these complications may be associated with a significant increase in TnT, its increase may simply be due to a violation of ventilation exchange and a decrease in oxygen delivery at the level of the myocardium. Today's elevated levels of TnT and natriuretic peptides increase the risk of death in ICU (Intensive Care Unit) with invasive ventilation, acute heart failure, compensatory hypertension and severe arrhythmic complications [11,12]. Clinical manifestations and cardiovascular complications may include a wide range of events related to the site of immunothrombosis; Although pulmonary complications are more common, other systems may also be involved in the spread of the virus. Organs that cause the disease are organs with increased blood perfusion, in which a high concentration of the virus can circulate. It should be noted that the coronary arteries and cardiac compartments, the cerebrovascular system and the kidneys are the areas where the virus can cause clinical complications due to direct poisoning or endothelial dysfunction, which are located in different areas, leading to thrombotic events and multi-organ failure [13, 14].

The purpose of the study. The purpose of this work is to study the causes and pathomorphology of thromboembolism in coronavirus infection according to the data of autopsy studies and statistical analysis of the pathological anatomy of complications.

Material and methods. The main cause of the disease based on autopsy results of 111 patients with thromboembolic complications caused by coronavirus infection, were analyzed retrospectively. The age of the dead patients ranged from 20 to 70 years old, including: 19 people with diabetes, 5 people with pregnancy, 31 people with ischemic heart disease, 24 people with COPD, 1 person with kidney disease, 26 people with heart disease, 1 person with cirrhosis of the liver and 4 patients with atherosclerosis.

The dead patients were divided into 5 groups according to gender and age: group 1 included patients aged 21 to 30 years: women (6 cases) men (2 cases); In 2-nd groups, women aged 31 to 40 years (10 cases) and men (14 cases); In 3-rd groups, women aged 41 to 50 years (10 cases) and men (13 cases); In 4-th group, women aged 51 to 60 years (11 cases) and men (15 cases), and in 5-th group women (12 cases) aged 61 to 70 years and men (18 cases). Autopsy was performed by Shor's method. All internal organs were taken for histological examination and their slices with a thickness of 0.5-1.0 cm and 1 cm2 were processed with 10 percent neutral formalin in a room temperature for 24-48 hours.

Results and discussion. 9 cases with pulmonary artery thromboembolism as the main cause of death were identified, which is 8.1 percent out of 111 cases.

There is a correlation of thrombosis level in relation to the sex and age of the deceased patients: thus, from 21 to 30 years old - 7.3 percent (8 cases); 31 to 40 years old - 21.6 percent (24 cases); 41 to 50 years old - 20.7 percent (23 cases); From 51 to 60 years old - 23.4 percent (26 cases) and from 61 to 70 years old - 27 percent (30 cases). The highest incidence rate of the disease is women and men aged 61 to 70 years, 12 cases in women and 18 cases in men. Because at this time, many other somatic diseases such as diabetes mellitus, IHD, etc. appeared together in women and men. The lowest point of incidence was between ages of 21 and 30, which was 6 in women and 2 in men.

Monitoring of patients in relation to gender; It was found that 44.1% (49 cases) in women infected with coronavirus infection and 55.9% (62 cases) of men died from complications of thrombosis. According to the occurrence of somatic diseases in patients who died from complications of thrombosis due to coronavirus infection: diabetes mellitus 17.1 percent (19 cases), pregnancy 4.5 percent (5 cases), ischemic heart disease 28.0 percent (31 cases), acute cerebral blood circulation disturbance 21,6 percent (24), kidney disease 0.9% (1), liver disease 23.4% (26), liver cirrhosis 0.9% (1) and atherosclerosis 3.6% (4) organized.

Ischemic heart disease took the first place among infectious diseases - 28.0 percent (31 cases). After that, hypertension disease - 23.4 percent (26 cases).

In our study, there were 3 cases of death due to complications of sinus thrombosis, morphologically, the combination of necrotic process in the nasal cavity with sinusitis in the upper respiratory tract, soft and hard palates.

Summary

1. Among the 111 patients who died from thromboembolic complications during the period from 2019 to 2021 as part of the coronavirus infection, 9 of them, i.e. 8.1%, have died from pulmonary artery thromboembolism.

2. The highest incidence rate of the disease in women and men aged 61 to 70 years, 12 cases in women and 18 in men. The lowest incidence point was between the ages of 21 and 30, cases - 6 for women and 2 for men.

3. By gender: 44.1 percent (49 cases) in women and 55.9 percent (62 cases) in men.

4. According to the occurrence of somatic diseases combined with infectious diseases: the first place was occupied by ischemic heart disease - 28.0 percent (31 cases). After that, hypertension disease took 23.4 percent (26 cases).

REFERENCES

1. Erkin N. Bilalov, Laziz N. Tuychiev, Shukhrat A. Baymuradov, Okil I. Oripov, Bakhodir E. Bilalov, Rajab Israilov, Azamat Yusupov, Akhmadjon Nozimov. CAVERNOUS SINUS THROMBOSIS ASSOCIATED WITH COVID-19. //Journal of Hunan University (Natural Sciences). October 2021. Vol. 48. No. 10

2. Zumrad Abduqayumovna Ergasheva, Rajabboy Israilovich Israilov, Alisher Kayumovich Shadmanov, Zukhriddin Salokhiddinovich Salokhiddinov, Mamazair Akhmedovich Khujamberdiev, Sardor Shakirov, Abdukhalim Khaliddin Ugli. Morfologicheskie osobennosti changes in the cardiovascular system during COVID-19. // Re-Health Journal #4 (12)-2021. 52-61.

3. Israilov R. PATHOMORPHOLOGY OF PULMONARY DISEASE WITH COVID-19. //A new day in medicine. – 2021. - #6(38). - pp. 186-194.

4. Pan A., Liu L., Wang C., Guo H., Hao X., Wang Q., Huang J., He N., Yu H., Lin X., et al. Association of Public Health Interventions with the Epidemiology of the COVID-19 Outbreak in Wuhan, China. JAMA. 2020;323:1915–1923. doi: 10.1001/jama.2020.6130. - DOI - PMC - PubMed

5. Frantzeskaki F. Immunothrombosis in acute respiratory distress syndrome: Cross talks between inflammation and coagulation. Respiration. 2017;93:212–225. doi: 10.1159/000453002.

6. Lopez-Castaneda S., García-Larragoiti N., Cano-Mendez A., Blancas-Ayala K., Damian-Vázquez G., Perez-Medina A.I., Chora-Hernández L.D., Arean-Martínez C., Viveros-Sandoval M.E. Inflammatory and Prothrombotic Biomarkers Associated with the Severity of COVID-19 Infection. Clin. Appl. Thromb. Hemost. 2021;27:1076029621999099. doi: 10.1177/1076029621999099.

7. Cui S., Chen S., Li X., Liu S., Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J. Thromb. Haemost. 2020;18:1421–1424. doi: 10.1111/jth.14830.

8. Bryce C., Grimes Z., Pujadas E., Ahuja S., Beasley M.B., Albrecht R., Hernandez T., Stock A., Zhao Z., AlRasheed M.R., et al. Pathophysiology of SARS-CoV-2: The Mount Sinai COVID-19 autopsy experience. Mod. Pathol. 2021;1:1–12. doi: 10.1038/s41379-021-00793-y.

9. Xu Z., Shi L., Wang Y., Zhang J., Huang L., Zhang C., Liu S., Zhao P., Liu H., Zhu L., et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 2020;8:420–422. doi: 10.1016/S2213-2600(20)30076-X.

10. Pennisi M., Lanza G., Falzone L., Fisicaro F., Ferri R., Bella R. SARS-CoV-2 and the Nervous System: From Clinical Features to Molecular Mechanisms. Int. J. Mol. Sci. 2020;21:5475. doi: 10.3390/ijms21155475.

11. D'Ascenzo F., De Filippo O., Borin A., Barbieri L., Adamo M., Morici N., Giachet A.T., Iannaccone M., Crimi G., Gaido L., et al. Impact of COVID-19 pandemic and infection on in hospital survival for patients presenting with acute coronary syndromes: A multicenter registry. Int. J. Cardiol. 2021 doi: 10.1016/j.ijcard.2021.03.063. in press.

12. Evans P.C., Rainger G.E., Mason J.C., Guzik T.J., Osto E., Stamataki Z., Neil D., Hoefer I.E., Fragiadaki M., Waltenberger J., et al. Endothelial dysfunction in COVID-19: A position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. Cardiovasc. Res. 2020;116:2177–2184. doi: 10.1093/cvr/cvaa230.

13. Madewell Z.J., Yang Y., Longini I.M., Jr., Halloran M.E., Dean N.E. Household Transmission of SARS-CoV-2: A Systematic Review and Meta-analysis. JAMA Netw. Open. 2020;3:e2031756. doi: 10.1001/jamanetworkopen.2020.31756.

14. Liu P.P., Blet A., Smyth D., Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. Circulation. 2020;142:68–78. doi: 10.1161/CIRCULATIONAHA.120.047549.