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M.O. Mykhailichenko[1], V.S. Melnyk[2], T.I. Halenova[3], N.G. Raksha[3], T.B. Vovk[3], L.I. Kot[3], O.O. Savchuk[3], L.I. Ostapchenko[3]
[1]University Clinic of the Bogomolets National Medical University, Kyiv, Ukraine
[2]Bogomolets National Medical University, Kyiv, Ukraine
[3]Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

Assessment of hemostatic changes in patients with chronic cerebral ischemia after recovery from COVID-19

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Abstract. ***Background.*** *COVID-19 is associated with disorders in the blood coagulation system that may persist beyond the acute phase of the disease, particularly in individuals with pre-existing cerebrovascular conditions. This research purposed to evaluate changes in key parameters of the procoagulant, anticoagulant, and fibrinolytic links of the hemostatic system in patients with chronic cerebral ischemia (CCI) following recovery from COVID-19.* ***Materials and methods.*** *The study involved 100 patients aged 43 to 74 years diagnosed with CCI and divided into two experimental groups: the CCI + COVID-19 group, which included 60 patients with a history of COVID-19, and the CCI group, consisted of 40 patients without SARS-CoV-2 infection in the past. Plasma levels of hemostatic markers, such as prothrombin, protein C, thrombomodulin, plasminogen, tissue plasminogen activator, plasminogen activator inhibitor-1, and von Willebrand factor, were measured using enzyme-linked immunosorbent assay.* ***Results.*** *The study did not observe significant differences in prothrombin or protein C levels between CCI patients with and without a history of COVID-19. However, there was a 20.9 % increase in plasma thrombomodulin levels in participants with CCI who had recovered from COVID-19 compared to those without prior infection. An increase in plasminogen activator inhibitor-1 content by 19.4 % was found in the CCI + COVID-19 group compared to the CCI group, while no significant differences in the levels of plasminogen and its tissue activator were established. Notably, von Willebrand factor levels did not show statistically significant differences between the groups, which could indicate a gradual correction of endothelial disturbances in post-COVID-19 over time.* ***Conclusions.*** *The data obtained indicate the complexity of post-COVID-19 hemostatic changes in patients with CCI, characterized by persistent low-grade inflammation and possible fibrinolysis inhibition. At the same time, the results suggest that endothelial dysfunction may not be a pronounced feature in the late post-COVID-19 period.*

Keywords: *chronic cerebral ischemia; post-COVID-19; SARS-CoV-2 infection; hemostatic system; coagulation; fibrinolytic system*

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become one of the greatest challenges for modern medicine, affecting not only the course of acute infectious processes but also leaving long-term consequences for the health of patients [1]. It is estimated that at least 65 million people worldwide suffer from long COVID-19, with the number of cases continuing to rise daily [2]. Unprecedented global efforts are currently underway to conduct clinical and fundamental research aimed at a detailed understanding of the pathogenetic mechanisms and risk factors of

Для кореспонденції: Кот Лариса Іванівна, кандидат біологічних наук, провідний фахівець навчальної міжкафедральної лабораторії інструментальних методів в біології, асистент, кафедра біохімії, Навчально-науковий центр «Інститут біології та медицини», Київський національний університет імені Тараса Шевченка, вул. Володимирська, 64/13, м. Київ, 01601, Україна; e-mail: kot_lora@ukr.net
For correspondence: Larysa Kot, PhD in Biological Sciences, Leading Specialist of the Educational Interdepartmental Laboratory of Instrumental Methods in Biology, Assistant, Department of Biochemistry, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Volodymyrska st., 64/13, Kyiv, 01601, Ukraine; e-mail: kot_lora@ukr.net
Full list of authors' information is available at the end of the article.

the prolonged course of COVID-19 and its complications. Special attention is being focused on studying comorbid conditions and chronic complications affecting various organs and systems, particularly the nervous system [3, 4]. Reports of debilitating neurological symptoms associated with post-acute sequelae of COVID-19, which encompass a wide range of pathologies, including general fatigue, headaches, cognitive impairments ("brain fog"), psycho-emotional disorders, strokes, microangiopathies, encephalopathies, and seizures, are constantly increasing [5, 6].

Chronic cerebral ischemia (CCI) is one of the most prevalent cerebrovascular diseases, accounting for approximately 60 % of all pathologies in this category. Unlike acute ischemia, which is a sudden and severe reduction in blood flow often leading to stroke, chronic ischemia is a slowly progressive condition characterized by prolonged microcirculatory disorders, decreased brain tissue perfusion, and neuroinflammation [7]. The relationship between CCI and post-acute sequelae of SARS-CoV-2 infection requires special attention, as these pathological states may potentially mutually reinforce each other, increasing the severity and progression of complications associated with cerebral blood flow disturbances [8, 9]. Furthermore, both COVID-19 and CCI are age-related diseases, and elderly individuals are at greater risk [10].

Recent studies propose several hypotheses regarding the pathogenesis of post-COVID-19 symptoms [11, 12]. These include the persistence of viral material, immune response dysregulation, increased permeability of the blood-brain barrier, endothelial dysfunction, and imbalance of cytokine profile, which promotes systemic inflammation and triggers coagulation cascades, causing prothrombotic events. Undoubtedly, there is a close interaction between these numerous mechanisms, and all of these factors may negatively affect cerebral hemodynamics, accelerating the progression of CCI [3].

The hemostatic system plays a key role in the pathogenesis of both CCI and the clinical manifestations of COVID-19, influencing the course of the acute phase of the disease, as well as the condition of patients in the post-infectious period [13, 14]. Hemostasis, as is known, is a finely tuned physiological process maintained by interconnected structural and functional links: procoagulant, anticoagulant, and fibrinolytic. Disruptions in the balance between these hemostatic components, along with increased activity of blood cells, in particular platelets, create conditions conducive to the development of coagulopathies and elevate the risk of thromboembolic complications, especially in patients with CCI. It is worth noting that coagulopathy associated with COVID-19 is a life-threatening complication of infectious disease [15]. However, the molecular mechanisms underlying this condition, especially in post-COVID-19 syndrome, remain incompletely understood.

Thus, studying changes in the hemostatic system in patients with CCI who have had a SARS-CoV-2 infection is of critical importance. Such research not only deepens the understanding of the pathophysiological mechanisms underlying these conditions but also paves the way for the development of new diagnostic approaches and effective therapeutic strategies, thereby mitigating thrombotic risks and preventing severe complications.

The purpose of the research was to assess the changes in the key parameters of the procoagulant, anticoagulant, and fibrinolytic links of the hemostatic system, including the levels of prothrombin, protein C, soluble thrombomodulin (TM), plasminogen, tissue-type plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), and von Willebrand factor (vWF), in CCI patients after recovery from COVID-19.

Materials and methods

The study involved 100 patients aged 43 to 74 years with stage III chronic cerebral ischemia who were divided into two experimental groups. The main group (CCI + COVID-19) included 60 participants (22 males and 38 females) with a mean age of 58.3 ± 5.6 years. They had CCI and experienced symptomatic COVID-19 9–12 months prior to the examination. The presence of SARS-CoV-2 infection was confirmed using a real-time reverse transcription polymerase chain reaction on nasopharyngeal swab samples and/or SARS-CoV-2 antibody tests. The control group (CCI) included 40 individuals (18 males and 22 females) with a mean age of 61.3 ± 7.5 years who had CCI but no history of COVID-19. All participants were patients of the University Clinic at the Bogomolets National Medical University (Kyiv, Ukraine). A medical history was obtained, and comprehensive general clinical, clinical-neurological, instrumental, neuropsychological, and laboratory assessments were conducted. We excluded individuals who had severe comorbid conditions, hematological, endocrinological, and oncological diseases, bleeding events within the past 6 months, a history of acute cerebrovascular accidents, or diabetes mellitus. All patients provided voluntary written informed consent to participate in the research. The study complied fully with the ethical and legal requirements of the Ministry of Health of Ukraine and the principles outlined in the Declaration of Helsinki (1964). The Ethical Committees of the Educational and Scientific Center "Institute of Biology and Medicine" of the Taras Shevchenko National University of Kyiv (Kyiv, Ukraine) and the Bogomolets National Medical University (Kyiv, Ukraine) approved the study.

Plasma for analysis was obtained from blood samples stabilized with sodium citrate (at the ratio of 9 : 1 v/v). Within 3 hours of collection, the samples were centrifuged at 2500 g for 15 minutes. The plasma was aliquoted and stored at –80 °C until use.

The levels of prothrombin, protein C, TM, plasminogen, tPA, PAI-1 and vWF in plasma samples were determined using enzyme-linked immunosorbent assay (ELISA) with specific monoclonal antibodies (Santa Cruz Biotechnology, Inc., USA). Blood plasma samples were diluted in a ratio of 1 : 100 with 0.05 M Tris-HCl buffer (pH 7.4), added to ELISA plate wells, and incubated at 37 °C for 1 hour. To remove non-specifically bound molecules, the samples were washed with 0.05 M Tris-HCl buffer (pH 7.4) containing 0.05% Tween-20. Free binding sites on the ELISA plate were blocked by adding 3% non-fat dry milk after incubation with the test antigens, followed by overnight incubation and

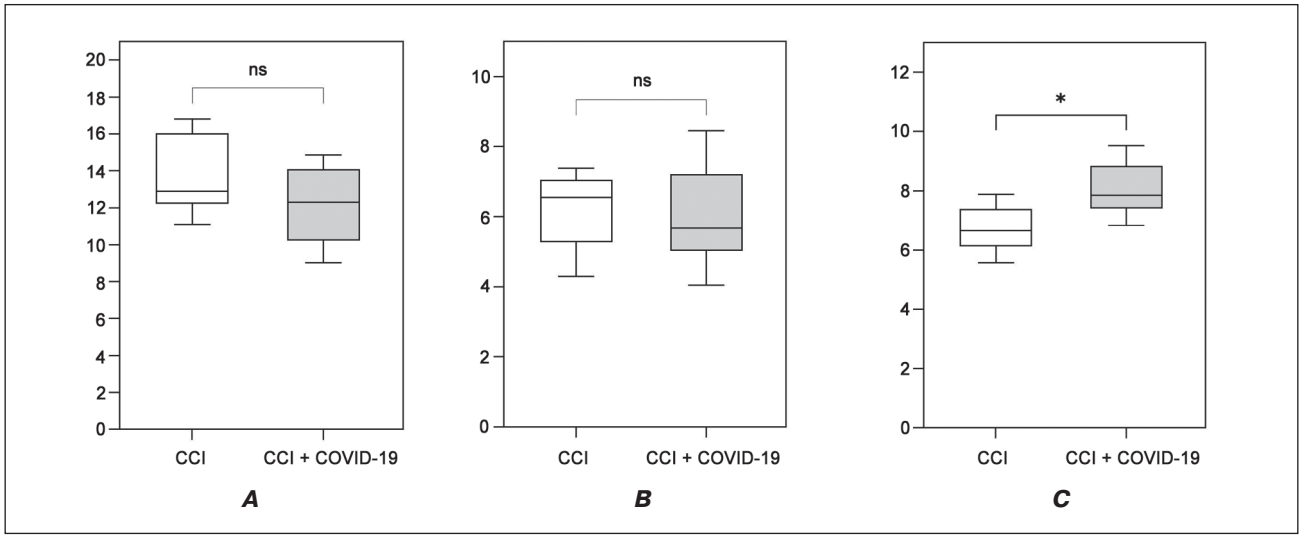

Figure 1. The levels of prothrombin (A), protein C (B), and TM (C) in plasma of CCI patients following COVID-19, relative units/ml

Notes: here and in Fig. 2: data are presented as a box-and-whisker plot displaying the median, IQR, minimal to maximal values; * — a difference between the groups ($p < 0.05$); ns — non-significant differences correspond to comparisons with $p \geq 0.05$.

subsequent washing steps. Primary and secondary antibody solutions were prepared according to the manufacturer's instructions. Plates were coated with monoclonal antibodies targeting specific antigens and incubated for 1 hour at 37 °C. Subsequently, the plates were incubated with horseradish peroxidase-conjugated secondary antibodies (Sigma-Aldrich, USA) for 1 hour at 37 °C. The enzymatic reaction was initiated using o-phenylenediamine and hydrogen peroxide (Sigma-Aldrich, USA) as substrates and terminated with 2.5 M H_2SO_4. Optical density was measured at 492 nm using a μQuant™ microplate spectrophotometer (BioTek Instruments, Inc., USA).

Statistical analysis was performed using GraphPad Prism software version 9.5.1 (GraphPad Software Inc., USA). The hypothesis of normal distribution was checked using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparisons between groups were performed with the unpaired Student's t-test for parametric data and the Mann-Whitney U test for nonparametric data. Data are expressed as median and interquartile range (IQR). Differences were considered statistically significant at $p < 0.05$.

Results and discussion

Hemostasis is maintained through the interaction of cellular components of whole blood, the vascular endothelium, pro- and anticoagulant plasma proteins, with the overall hemostatic state depending on the balance between coagulation and fibrinolysis [16]. COVID-19 is characterized by disruptions in all phases of hemostasis due to systemic inflammation, endothelial dysfunction, and activation of the coagulation cascade, which may persist for an extended period after the acute phase of the disease [17]. Our previous research [18] found that the post-COVID-19 was associated with an increased risk of coagulation dysfunction in groups with various titers of anti-SARS-CoV-2 IgG. Despite abnormalities detected in routine coagulation tests among patients recovering from COVID-19, growing evidence suggests a tendency toward the restoration of balance between procoagulant and anticoagulant activity. In most cases, these patients exhibit a mildly altered yet stable hemostatic state [19]. Compensatory mechanisms may temporarily counterbalance these disturbances, resulting in a "rebalancing" of the coagulation system in those who have experienced SARS-CoV-2 infection. However, this compensatory capacity has its limits, and prolonged inflammation or the presence of comorbid conditions, such as cerebrovascular diseases, can disrupt the hemostatic balance. This may lead to an increased risk of thrombosis, ischemic stroke, or other complications associated with cerebral hemodynamic impairment [20].

Since the hemostatic system plays a crucial role in the pathogenesis of both CCI and post-COVID-19, this research aimed to analyze changes in the levels of its key components. In particular, prothrombin, TM, protein C, plasminogen, tPA, PAI-1, and vWF are markers that reflect the state of the procoagulant, anticoagulant, and fibrinolytic systems. In patients with CCI who recovered from COVID-19 several months ago, changes in these markers may indicate a disruption in hemostatic balance, contributing to the progression of ischemic damage.

The procoagulation activity was evaluated by the level of prothrombin, one of the key circulating proteins in the blood coagulation system. The results revealed no significant differences in the plasma levels of this parameter between patients with CCI who had a history of COVID-19 and those without prior SARS-CoV-2 infection (Fig. 1A). These findings suggest that COVID-19 may not have a direct or long-lasting impact on the procoagulant pathway in patients with CCI.

Prothrombin is a crucial protein in the coagulation cascade, playing a central role in thrombin formation, which

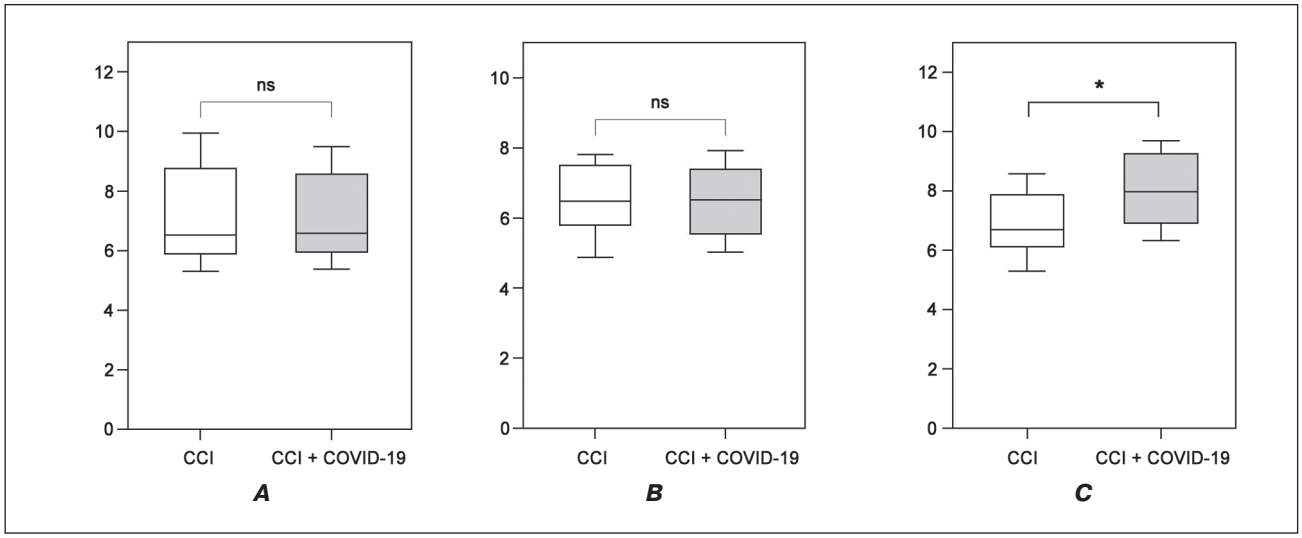

Figure 2. The levels of plasminogen (A), tPA (B), and PAI-1 (C) in plasma of CCI patients following COVID-19, relative units/ml

is essential for clot formation and maintaining hemostasis. The absence of significant changes in prothrombin levels in the post-COVID-19 period indicates that, despite the prothrombotic effects associated with COVID-19, the virus may not cause long-term disruptions in prothrombin content in CCI patients. Additionally, other compensatory mechanisms within the coagulation system may help mitigate any potential COVID-19-induced alterations, maintaining a stable hemostatic balance over time [19]. While COVID-19 has been linked to acute and severe coagulopathies, including an increased risk of thrombosis and elevated procoagulant factors, these alterations are often transient and may normalize after the acute infection phase. Moreover, other comorbid conditions commonly present in CCI patients, such as hypertension or atherosclerosis, may have a more pronounced effect on coagulation and hemostatic balance than COVID-19 itself [21].

The anticoagulant link of hemostasis was assessed by the levels of protein C and TM. It was shown that in patients with CCI following COVID-19, the plasma TM level increased by 20.9 % compared to people with CCI who had no history of SARS-CoV-2 infection ($p < 0.01$) (Fig. 1C). However, no significant differences were observed in the level of protein C between the CCI and CCI + COVID-19 groups (Fig. 1B). The observed increase in plasma TM level in patients with CCI who had COVID-19 could reflect a lasting impact of its acute phase on the anticoagulant system, during which an increased anticoagulant response occurs.

TM is a transmembrane glycoprotein expressed on the surface of all vascular endothelial cells and serves as a key regulator of thrombin. It functions as an anticoagulant by activating protein C, thereby inhibiting thrombin-induced clot formation. An increase in TM levels may suggest a compensatory response to mitigate any residual hypercoagulable states that could have been triggered by COVID-19, even 9–12 months after the acute infection. However, the lack of significant differences in protein C levels indicates that its activation may not have been significantly altered in these patients or compensated by other factors in the coagulation system. These results could suggest that the hemostatic imbalance in CCI patients with a history of SARS-CoV-2 infection is more likely related to endothelial cell dysfunction rather than changes within the anticoagulant system itself. An increase in the level of TM is consistent with our previous studies [22], which examined hemostatic system changes in multiple sclerosis patients with a history of COVID-19. These changes were associated with the presence of a soluble form of TM in circulation, formed as a result of increased endothelial cell damage and intensified inflammation [22, 23].

To assess the potential of the fibrinolysis system in CCI patients following COVID-19, we determined the level of plasminogen, tPA, and PAI-1. Changes were observed only in the plasma PAI-1, which increased by 19.4 % in CCI patients who had recovered from COVID-19 compared to those without a history of viral infection ($p < 0.007$) (Fig. 2C). It should be noted that the levels of plasminogen and its tissue activator showed no significant differences between the CCI and CCI + COVID-19 groups (Fig. 2A, 2B).

PAI-1 plays a crucial role in regulating fibrinolysis by inhibiting tPA and urokinase-type plasminogen activator, which are responsible for converting plasminogen into plasmin and promoting fibrin clot breakdown [24]. The increased level of PAI-1 in patients who had recovered from COVID-19 is consistent with the known prothrombotic effects of the SARS-CoV-2 [25]. This finding aligns with studies in COVID-19 patients, which have identified hypercoagulability as a common feature contributing to complications, such as thrombosis and other thromboembolic events [26]. Moreover, alterations in the fibrinolytic system components may depend on the titers of circulating anti-SARS-CoV-2 IgG in the bloodstream [27].

The sustained elevation of PAI-1 in the post-COVID-19 may reflect a lingering effect of the acute infection, with the inflammatory response and endothelial dysfunction continue to influence hemostatic regulation even long af-

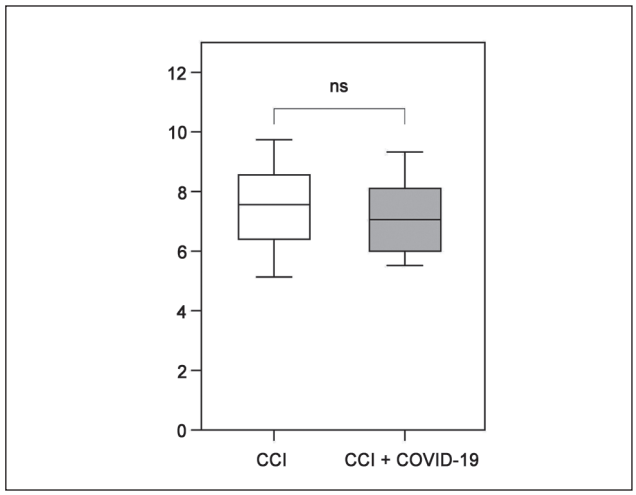

Figure 3. The level of vWF in plasma of CCI patients following COVID-19, relative units/ml

Notes: data are presented as a box-and-whisker plot displaying the median, IQR, minimal to maximal values; ns — non-significant differences correspond to comparisons with p ≥ 0.05.

ter recovery. Inflammation and endothelial damage induced by COVID-19 can lead to upregulation of PAI-1 secretion, which promotes clot stability by inhibiting fibrinolysis, thus impairing the breakdown of fibrin clots. This is particularly relevant in patients with CCI in whom the disruption of the delicate balance between clot formation and dissolution can exacerbate ischemic damage. It is also possible that an increase in PAI-1 level reflects a chronic, low-grade inflammatory response that persists after COVID-19, as PAI-1 is known to be upregulated during inflammatory states [28]. The absence of statistically significant changes in plasminogen and tPA levels in CCI patients who had recovered from COVID-19 may indicate that the fibrinolytic system remains relatively stable in the chronic post-COVID phase, in the absence of infection and acute inflammatory reaction, despite the elevated levels of PAI-1. This may indicate a subtle shift in the fibrinolytic balance toward thrombus stability, highlighting a more complex interaction between prothrombotic and fibrinolytic mechanisms in post-COVID-19 patients with chronic conditions, such as CCI.

Given the minor deviations observed in the levels of key components of the procoagulant, anticoagulant, and fibrinolytic systems, we evaluated vWF level as a marker of endothelial function and vascular integrity. Endothelial dysfunction, a characteristic feature of both CCI and post-COVID-19 conditions, can contribute to the onset or progression of coagulation abnormalities [29]. vWF is either constitutively produced or released from Weibel-Palade bodies of endothelial cells, stored platelets, and subendothelial connective tissue in a high-molecular-weight, long multimeric form. This multimeric vWF associates with factor VIII molecules, promoting platelet adhesion and thrombus formation, and serves as a critical indicator of endothelial function and the maintenance of hemostatic balance [30]. In our research, no significant differences in vWF levels were found between the CCI and CCI + COVID-19 groups (Fig. 3). This suggests that endothelial dysfunction in the post-COVID-19 phase may not be pronounced, or that any COVID-19-induced endothelial disturbances have largely resolved over time. Alternatively, vWF level may be influenced by regulatory mechanisms unrelated to COVID-19 in this cohort, or the endothelial alterations may be too subtle or localized to be detected by this marker alone.

Conclusions

Thus, our findings highlight the complexity of post-COVID-19 hemostatic changes in patients with CCI. The persistence of elevated TM and PAI-1 levels could indicate an ongoing low-grade inflammation, which may still contribute to an increased thrombotic risk, particularly in individuals with comorbid conditions. In contrast, the lack of significant changes in plasminogen and its tissue activator, despite an increase in PAI-1 levels, indicates a potential shift toward fibrinolysis inhibition — likely as a compensatory response to the hypercoagulable state induced by COVID-19. Furthermore, vWF levels did not differ significantly between CCI patients with and without a history of SARS-CoV-2 infection, suggesting that endothelial dysfunction may not be a prominent feature in the late post-COVID-19 phase or that any endothelial disturbances have largely resolved over time. These findings emphasize the need for further research to better understand the long-term impact of COVID-19 on hemostasis and the vascular system, as well as to optimize management strategies for patients with cerebrovascular diseases following SARS-CoV-2 infection.

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Information about authors

Marina Mykhailychenko, Head of the Neurological Department, University Clinic of the Bogomolets National Medical University, Kyiv, Ukraine; e-mail: mail.neurologist.2023@gmail.com; https://orcid.org/0009-0001-1221-4220

Volodymyr Melnyk, MD, DSc, PhD, Professor, Department of Neurology, Dean of the Medical Faculty, Bogomolets National Medical University, Kyiv, Ukraine; e-mail: volodymyr.melnyk@nmu.ua; https://orcid.org/0000-0003-4645-8239

Tetiana Halenova, PhD in Biological Sciences, Senior Researcher, Assistant, Department of Biochemistry, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv, Ukraine; e-mail: galenovatanya@gmail.com; https://orcid.org/0000-0003-2973-2646

Nataliia Raksha, PhD in Biological Sciences, Senior Researcher, Assistant, Department of Biochemistry, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv, Ukraine; e-mail: nkudina@ukr.net; https://orcid.org/0000-0001-6654-771X

Tetiana Vovk, PhD, Department of Biochemistry, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv, Ukraine; e-mail: sanwoolf01@gmail.com; https://orcid.org/0000-0002-0440-8922

Larysa Kot, PhD in Biological Sciences, Leading Specialist of the Educational Interdepartmental Laboratory of Instrumental Methods in Biology, Assistant, Department of Biochemistry, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv, Ukraine; e-mail: kot_lora@ukr.net; https://orcid.org/0000-0002-8308-4902

Oleksii Savchuk, Student, Department of Biochemistry, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv, Ukraine; e-mail: oleksiisavchuk@knu.ua; https://orcid.org/0009-0005-3743-4763

Liudmyla Ostapchenko, Doctor of Biological Sciences, Professor, Department of Biochemistry, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv, Ukraine; e-mail: ostapchenko@knu.ua; https://orcid.org/0000-0001-7181-6048

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Михайліченко М.О.[1], Мельник В.С.[2], Галенова Т.І.[3], Ракша Н.Г.[3], Вовк Т.Б.[3], Кот Л.І.[3], Савчук О.О.[3], Остапченко Л.І.[3]
[1]Університетська клініка Національного медичного університету імені О.О. Богомольця, м. Київ, Україна
[2]Національний медичний університет імені О.О. Богомольця, м. Київ, Україна
[3]Навчально-науковий центр «Інститут біології та медицини» Київського національного університету імені Тараса Шевченка, м. Київ, Україна

Оцінка змін у системі гемостазу в пацієнтів із хронічною ішемією мозку після одужання від COVID-19

Резюме. ***Актуальність.*** COVID-19 асоціюється з порушеннями в системі згортання крові, які можуть зберігатися навіть після гострої фази хвороби, особливо в пацієнтів із наявними цереброваскулярними розладами. Дослідження спрямоване на оцінку змін основних показників прокоагулянтної, антикоагулянтної та фібринолітичної ланок системи гемостазу в осіб із хронічною ішемією мозку (ХІМ) після одужання від COVID-19. ***Матеріали та методи.*** У дослідженні взяли участь 100 пацієнтів віком від 43 до 74 років із діагнозом ХІМ, яких розподілено на дві експериментальні групи: групу «ХІМ + COVID-19» — 60 хворих, які перенесли COVID-19, та групу ХІМ — 40 осіб без інфекції SARS-CoV-2 в анамнезі. Плазмові рівні показників системи гемостазу, як-от протромбін, протеїн С, тромбомодулін, плазміноген, тканинний активатор плазміногену, інгібітор активатора плазміногену-1 та фактор фон Вілебранда, визначали за допомогою імуноферментного аналізу. ***Результати.*** У дослідженні не спостерігалося значних відмінностей у рівнях протромбіну та протеїну С між пацієнтами з ХІМ із COVID-19 та за відсутності його в анамнезі. Проте відмічалося збільшення на 20,9 % умісту тромбомодуліну в плазмі крові хворих на ХІМ, які перенесли COVID-19, порівняно з тими, хто не мав інфекції в анамнезі. Виявлено збільшення рівня інгібітора активатора плазміногену-1 на 19,4 % у групі «ХІМ + COVID-19» проти групи ХІМ, у той час як значних відмінностей у вмісті плазміногену та його тканинного активатора не встановлено. Важливо, що фактор фон Вілебранда не мав статистично значущих відмінностей між групами, що могло свідчити про поступову корекцію порушень ендотелію після COVID-19 із часом. ***Висновки.*** Отримані дані вказують на складність постковідних гемостатичних змін у пацієнтів із ХІМ, які характеризуються стійким запаленням низького ступеня та можливим інгібуванням фібринолізу. Водночас результати дозволяють зробити припущення, що ендотеліальна дисфункція може не бути вираженою ознакою в більш віддалені терміни після COVID-19.

Ключові слова: хронічна ішемія мозку; пост-COVID-19; інфекція SARS-CoV-2; система гемостазу; коагуляція; фібринолітична система