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Conflict of interest. The authors declare no conflicts of interest.

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Article received: 12.05.2025

DOI 10.26724/2079-8334-2026-2-96-140-144
UDC 612.115-06:616.28-008.1-02:616.98:578.834]-047.44

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ASSESSMENT OF BLOOD COAGULATION SYSTEM STATUS IN PATIENTS WITH SENSORINEURAL HEARING IMPAIRMENTS WHO HAVE RECOVERED FROM COVID-19

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COVID-19 is a systemic disease that affects various body systems, including the auditory system and the hemostatic system. Changes in platelet-vascular, coagulation, and fibrinolytic components of hemostasis were studied in 32 patients with sensorineural hearing impairments who had recovered from COVID-19 and 20 healthy individuals with normal hearing. Normalization of fibrinogen and ecarin time was established. An increase in soluble fibrin concentration was detected against the background of decreased D-dimer levels. This indicates the activation of the blood coagulation system and the inability of fibrinolysis to hydrolyze fibrin clots, which is indirectly confirmed by increased levels of RFMC. A decrease in protein C content was established, indicating intravascular thrombin generation, as a result of which there is an increase in prothrombin-1 and soluble fibrin concentration. Prolongation of activated partial thromboplastin time and prothrombin time against the background of changes in the aforementioned parameters is a manifestation of chronic consumptive coagulopathy. The absence of normalization of hemostasis parameters in patients who have recovered from COVID-19 is an unfavorable prognostic sign.

Key words: COVID-19, post-COVID syndrome, sensorineural hearing loss, hemostasis, soluble fibrin, chronic coagulopathy.

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ОЦІНКА СТАНУ СИСТЕМИ ЗСІДАННЯ КРОВІ У ПАЦІЄНТІВ ІЗ СЕНСОНЕВРАЛЬНИМИ ПОРУШЕННЯМИ СЛУХУ, ЯКІ ПЕРЕХВОРІЛИ НА COVID-19

COVID-19 є системним захворюванням, при якому уражаються різні системи організму, зокрема слухова і система гемостазу. Було досліджено зміни показників тромбоцитарно-судинної, коагуляційної та фібринолітичної ланок гемостазу у 32 пацієнтів з сенсоневральними порушеннями слуху, які перехворіли на COVID-19 та 20 здорових нормальночуючих осіб. Встановлена нормалізація фібриногену та екамулінового часу. Виявлено підвищення концентрації розчинного фібрину на тлі зниження Д-димеру. Це свідчить про активацію системи зсідання крові та не здатність фібринолізу гідролізувати фібринові згустки на що опосередковано підтверджує підвищення рівня РФМК. Встановлено зниження вмісту протеїну С, що вказує на внутрішньосудинну генерацію тромбіну. Внаслідок надпродукції якого відбувається підвищення претромбіну-1 й концентрації розчинного фібрину. Подовження активованого часткового тромбопластинового часу та протромбінового часу на тлі змін вищевказаних показників, є проявом хронічної коагулопатії споживання. Відсутність нормалізації показників гемостазу у пацієнтів, які перехворіли на COVID-19 є несприятливою прогностичною ознакою.

Ключові слова: COVID-19, постковідний синдром, сенсоневральна приглухуватість, гемостаз, розчинний фібрин, хронічна коагулопатія.

Funding. *The work is a fragment of the research project "Comprehensive clinical and instrumental characteristics of the state of sensory systems – auditory, olfactory and vestibular systems, as well as extraaural manifestations in COVID-19", state registration No. 0121U113546.*

COVID-19 is a systemic disease because, in addition to the respiratory system, it can also affect other body systems, including the cardiovascular, nervous, hematopoietic, gastrointestinal, immune, and others [5, 6]. There are reports in the literature of sensory system impairments in COVID-19, in particular the auditory system. Moreover, the reduction of auditory function, subjective ear noise, and the feeling of ear fullness may be caused by both

conductive and perceptive disorders in the auditory analyzer [9].

It is known that the course of COVID-19 is accompanied by patients' predisposition to thrombotic and thrombophilic complications, which are based on inflammation, activation of endothelial dysfunction, platelets, impaired functioning of the fibrinolysis system, and so on. Particularly severe conditions are associated with the development of disseminated intravascular coagulation, deep vein thrombosis, pulmonary artery embolism, and other coagulopathies. COVID-19-associated coagulopathy causes damage to various organs and can lead to multiple organ failure and death [2].

One of the features of COVID-19 is the development of post-COVID syndrome, in which disruptions occur in many body systems, including the hemostasis system. The duration of this pathological condition and the methods for identifying risk factors for complications currently require detailed study. Since the mechanisms of inflammation regulation and the hemostasis system are closely connected, identifying markers of the risk of intravascular thrombosis makes it possible to prevent thrombotic complications [1].

Sensorineural hearing impairments remain one of the pressing issues in otolaryngology. Sensorineural hearing loss (SNHL) is a multi-etiological disease, with the infectious factor playing a significant role in its occurrence and progression [3].

The purpose of the study was to investigate changes in the platelet-vascular, coagulation, and fibrinolytic components of hemostasis in patients with sensorineural hearing impairments who had recovered from COVID-19.

Materials and methods. The study was conducted at the State Institution "Institute of Otolaryngology named after Prof. O.I. Kolomiychenko of the National Academy of Medical Sciences of Ukraine" from July 2021 to November 2025.

Thirty-two patients with perceptual hearing impairments who had recovered from COVID-19 were examined. All patients were informed and provided written consent to participate in the research process in accordance with the World Medical Association's Code of Ethics, the WMA Declaration of Helsinki. At the time of blood collection, the patients had recovered from COVID-19, were seropositive, and did not have the pathogen in their blood according to PCR data. The control group included 20 healthy persons with normal hearing.

The object of the study was citrated blood plasma obtained by a standard method. The concentration of fibrinogen was determined using a spectrophotometric method with a thrombin-like enzyme. Activated partial thromboplastin time (APTT) was determined by the clotting time of blood plasma with standard contact phospholipid activation in the presence of calcium ions (test system "Renam-U", Ukraine). Prothrombin time (PT) was determined by initiating the polymerization of the plasma sample under study with an excess of tissue thromboplastin and calcium ions (test system "Siemens", USA). The overall level of prothrombin was assessed by ecamulin time (ET). Ecamulin is an enzyme that activates prothrombin, derived from the venom of the many-scaled viper (Echis multisquamatus), which activates both prothrombin and its functionally inactive forms, including prethrombin-1 (Pre-1). The method for determining the concentration of Pre-1 is based on the ratio between the coagulation time initiated by a non-physiological prothrombin activator and the coagulation time initiated by thromboplastin. Thus, a non-physiological prothrombin activator (Ecamulin) activates both intact prothrombin and its functionally inactive forms. Thromboplastin, which is used in the prothrombin time test, triggers the blood clotting cascade through the extrinsic pathway, which activates only intact prothrombin. The calculation of Pre-1 concentration was carried out using the formula obtained from the calibration curve (1),

$$C = \frac{\mathrm{EI}/\mathrm{PI} - 0.9919}{0.141} - 0.1, \qquad (1)$$

where C is the concentration of Pre-1, μg/mL; EI is the ecamulin index (the ratio of blood plasma clotting time of donors and patients, corresponding to the overall prothrombin level in blood plasma); PI is the prothrombin index (the ratio of blood plasma clotting time of donors and patients, corresponding to the level of intact prothrombin in blood plasma).

The content of protein C was determined by cleavage of the chromogenic substrate S2366 using protein C activator (Siemens test system, USA). The concentration of soluble fibrin (SF) was determined by the solid-phase enzyme immunoassay method using a monoclonal 'catch' antibody specific to desAB fibrin (I-3C) and a monoclonal 'tag' antibody specific to fibrinogen and its derivatives (II-4d). The D-dimer concentration was determined by a solid-phase enzyme immunoassay using a monoclonal 'catch' antibody specific to D-dimer (III-3B) and a monoclonal 'tag' antibody specific to fibrinogen and its derivatives (II-4d). The determination of soluble fibrin-monomer complexes (SFMC) was carried out using the semi-quantitative Belitzer-Varetska method. The absence of visible cloudiness was assessed as a negative result, transparent cloudiness as positive (+), corresponding to a content of 0.03 g/l, flake-like sediment (++) – 0.06 g/l, formation of flake-like and filamentous structures – (+++) – 0.09 g/l, gel-like sediment – (++++) – 0.12 g/l. The statistical processing of the results was carried out using the software package for statistical processing of biometric data WinPEPI. To assess the difference between patients and the control group, Student's t-test was used. Differences between groups were

considered significant if the level of statistical significance $p < 0.05$ was reached.

Results of the study. It is known that fibrinogen belongs to the acute-phase proteins, which are mainly synthesized in the liver, but are also contained in the alpha granules of platelets, from which they are secreted upon platelet activation. This explains the diverse role of this protein in the process of maintaining homeostasis. In particular, during inflammation, the role of fibrinogen is primarily due to reducing the risk of process generalization and protecting the body. Therefore, in patients with COVID-19, it is recommended to determine the concentration of fibrinogen. As a result of our studies, it was established that the level of fibrinogen in the blood plasma of patients with SNHL who had recovered from COVID-19 had returned to the levels of the control group (Table 1).

Table 1

Coagulation system indicators in the blood plasma of patients with SNHL who have recovered from COVID-19

Indicators	Groups of the examined	
	Practically healthy individuals	Patients with SNHL who have recovered from COVID-19
Fibrinogen, g/L	2.30±0.20	2.00±0.10
APTT, sec.	43.20±1.10	70.90±3.10*
Prothrombin time, sec.	14.00±1.00	29.80±1.20*
Ekamuline time, sec.	119.30±2 .20	121.30±9.70
Prothrombin-1, μg/mL	0.20±0.10	3.90±0.80*
Protein C, %	115.00±4.50	58.90±6.50*
D-dimer, ng/mL	70.00±6.30	54.20±6.32
Soluble fibrin, μg/ml	2.90±0.25	16.85±2.42*
SFMC, s.unit.	0	23.80±6.80*

Note: * – statistically significant difference between the group of practically healthy individuals and the corresponding indicators of patient groups ($p<0.05$ – $p<0.001$).

Activated partial thromboplastin time is an informative screening test that reflects changes in the activity of the intrinsic pathway coagulation factors and disturbances in the balance between the procoagulant and anticoagulant components of the hemostasis system. In the blood plasma of patients with SNHL who had recovered from COVID-19, a significant prolongation of APTT by 1.6 times was found compared to the control group. This may be related to a deficiency of high molecular weight kininogen, prekallikrein, blood clotting factors XII, XI, VIII, X, as well as fibrinogen/fibrin degradation products.

The determination of prothrombin time is necessary to assess the presence of a deficiency of the factors of the prothrombin complex and the extrinsic coagulation pathway or coagulation inhibitors. As can be seen from the data presented, PT in patients of the aforementioned group was significantly prolonged by 2.1 times compared to control values. This prolongation of the indicator may likely indicate the accumulation in blood plasma of compounds capable of reducing thrombin activity.

To determine the prothrombin content and detect its functionally inactive forms, the ecamulin time was measured. It was established that the ET level in the blood plasma of patients with SNHL who had recovered from COVID-19 almost returned to the levels of the control group. Functionally inactive form of prothrombin and a marker of its autolysis by thrombin, indicating activation of the blood coagulation system, is prothrombin-1. In the blood plasma of patients with SNHL who had COVID-19, a significant increase in Pre-1 by 19.5 times was detected compared to the control group, which may indicate a risk of intravascular thrombosis.

In response to the activation of the components of the blood clotting system and the development of an inflammatory process, protein C is activated, which is a key component of the anticoagulant system. As a result of the conducted studies, a probable twofold decrease in the content of protein C was established in patients of this group compared to the control group. The decrease in protein C content is a marker of a pre-thrombotic state.

The determination of D-dimer is a mandatory element in the diagnosis of pathologies associated with intravascular thrombosis. However, as a product of the hydrolysis of stabilized fibrin, D-dimer does not allow the detection of a thrombotic threat, but only indicates that a thrombus or fibrin deposit has already formed and is now undergoing hydrolysis by plasmin. This indicator should be considered as a post-thrombotic marker, and only the simultaneous quantitative determination of soluble fibrin and D-dimer makes it possible to comprehensively characterize the state of the patient's hemostatic system. The presented data show that the D-dimer concentration in patients with SNHL who recovered from COVID-19 was reduced by 1.3 times compared to the control, but at a trend level.

Changes in the concentration of soluble fibrin are an early prognostic indicator of intravascular coagulation activation, so determining its level is important for the prevention of intravascular thrombosis. In the blood plasma of patients with SNHL who have recovered from COVID-19, a significant increase in the concentration of SF by 5.8

times compared to normal was detected. The recorded changes indicate activation of the blood coagulation system and a risk of thrombosis. The detected decrease in D-dimer levels indicates the inability of the fibrinolytic system to cope with the degradation of both soluble fibrin and clots that may have already formed. Since it is well known that when there is a balance between the coagulation and fibrinolysis systems, the amount of D-dimer is always proportional to the amount of SF.

The determination of soluble fibrin-monomer complexes (SFMC), which are normally present in the bloodstream at minimal concentrations, is one of the main indicators of hypercoagulation status. It has been shown that the level of SFMC in blood plasma was significantly higher between the control group and the aforementioned patient group. This may indicate that the fibrinolysis system does not prevent the accumulation of fibrin clots in the vessels.

Discussion. According to the World Health Organization, most patients who have had COVID-19 return to their previous state of health. However, a number of data have been published indicating that approximately 10-20 % (according to some data, even up to 50 %) of patients experience malaise and have complications in various organ systems for a prolonged period, which becomes a reason for them to consult highly specialized specialists of various profiles [4].

In particular, in our previous studies, we identified changes in cerebral hemodynamics in patients with COVID-19 with hearing impairments [3]. Considering the vulnerability of the cardiovascular system to the effects of the SARS-CoV-2 virus, as well as the sensitivity of the auditory analyzer to vascular disorders, we continued our research in terms of assessing the condition of the hemostatic system in such patients. The patients examined in this study had sudden and acute SNHL as a result of COVID-19, or a significant progression of pre-existing hearing loss.

A risk factor for the development of intravascular thrombosis is an increase in the concentration of fibrinogen – the precursor of fibrin – in the patient's blood plasma. Experts of the International Society on Thrombosis and Haemostasis (ISTH) during the pandemic did not indicate the need to measure fibrinogen concentration in every COVID-19 patient at the time of hospitalization. However, according to a number of authors, this parameter should be taken into account when assessing the hemostatic system in patients with COVID-19. Since a sudden decrease in plasma fibrinogen to concentrations below 1.0 g/L was observed shortly before death in a number of patients with COVID-19 [1, 7, 11], in patients with SNHL who had recovered from COVID-19 and participated in our study, the fibrinogen level normalized.

The product of fibrinogen cleavage by thrombin is monomeric fibrin, which can form complexes with fibrinogen and its derivatives without the formation of solid-phase fibrin. Oligomers of fibrin and fibrinogen, which circulate freely in the bloodstream, are called soluble fibrin, which is considered one of the main markers of the risk of intravascular thrombosis [1]. The established accumulation of SF concentration in the above-mentioned group of patients indicates the activation of the blood coagulation system in their body.

The overall level of prothrombin was assessed using ecarin clotting time. The data we obtained indicate that in patients with SNHL who have recovered from COVID-19, the content of functional prothrombin has returned to the levels of the control group. However, at the same time, they showed a decrease in protein C content against the background of an increase in soluble fibrin concentration, which may indicate intravascular thrombin generation [12]. The consequence of thrombin overproduction is an increase in the concentration not only of SF, but also of prothrombin-1 in the blood plasma of patients who participated in our study. Normally, prothrombin is converted into thrombin during the blood clotting process. If prothrombin is normal while thrombin is elevated, this may indicate activation of blood coagulation outside the normal physiological process. Thus, the lack of normalization of the above indicators indicates a high risk of intravascular thrombosis in this group of patients [1].

According to the literature, to assess the condition of patients and determine the prognosis of COVID-19, fibrinogen should be compared with the fibrin degradation product – D-dimer. Moreover, only the simultaneous determination of the concentrations of soluble fibrin and D-dimer can provide information on whether fibrin deposits existed in the circulation, whether they are currently forming, and whether they are being degraded by the fibrinolysis system. The detected decrease in D-dimer concentration against the background of elevated SF in the plasma of patients with SNHL who have recovered from COVID-19 may indicate the presence of fibrin deposits that are not hydrolyzed by the fibrinolytic system and pose a threat of ischemia and embolism. In addition, the fact that the fibrinolytic system does not prevent the accumulation of fibrin clots in the vessels is indirectly indicated by the increased level of SFMC in the blood of this group of patients [1, 13].

Activated partial thromboplastin time is among the recommended tests to be conducted for patients with COVID-19 who are hospitalized [7]. In particular, in the study by Tang et al., APTT was significantly prolonged in the group of COVID-19 patients who later died compared to the group of patients who survived [10]. Prothrombin time is one of the indicators that ISTH recommends measuring in all patients with COVID-19 [11]. Reliable prolongation of APTT and PT, against the background of normalization of fibrinogen levels in patients with chronic heart failure who have had

COVID-19, may be associated with an inflammatory response caused by cytokines. The mechanism of hypercoagulation is multifactorial and is likely induced by direct viral damage to the vascular endothelium, caused by cytokines, leading to the activation of platelets, monocytes, macrophages, increased expression of tissue factor, von Willebrand factor, and factor VIII, which can lead to thrombus formation and the development of a fibrin clot [8].

Conclusion

As follows from the presented data, changes in the parameters of the platelet-vascular, coagulation, and fibrinolytic links of hemostasis in patients with sensorineural hearing impairments who have had COVID-19 are complex and multidirectional in nature.

It was established that out of 9 studied indicators, only 2 returned to the normal level, namely the fibrinogen level and eculine time, which indicates the absence of inflammation and the normalization of functional prothrombin content. The observed increase in the concentration of soluble fibrin against the background of a decrease in D-dimer indicates activation of the blood coagulation system and the inability of the fibrinolysis system to hydrolyze fibrin clots, which is also indirectly evidenced by the increased level of SFMC.

The established decrease in protein C content indicates intravascular thrombin generation. As a result of its overproduction, there is an increase in Pre-1 and SF concentrations. Detected prolongation of APTT and PT against the background of changes in the above indicators should be considered as a manifestation of chronic consumption coagulopathy. This indicates depletion of the coagulation factor pool due to their constant use in microthrombosis processes, which significantly increases the procoagulant potential of the blood and poses a risk of ischemic complications.

The lack of normalization of hemostasis indicators in patients who have recovered from COVID-19 is an unfavorable prognostic sign and is a reason for them to consult specialized medical facilities for corrective therapy in the post-COVID period.

Prospects for further research. In this clinical direction, it is planned in the further perspective to study the possible impact of COVID-19 on other structural elements of the auditory and vestibular analyzers. The research will concern both the peripheral sections and various areas of the VIII cranial nerve pair and the corresponding elements of the central structures of the brain and cerebellum.

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Conflict of interest. The authors have no conflicts of interest to declare.

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Article received: 7.04.2025