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ABSTRACT
of the PhD DOCTORAL DISSERTATION

Topic title: "**The study of neurological aspects of COVID-19 in the acute and post-COVID periods**"

According to the educational program 8D10102 "Medicine"
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Completion dates: 2019-2022

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Aktobe, 2025

ABSTRACT

Jumagaliyeva M.B. on the topic: "The study of neurological aspects of COVID-19 in the acute and post-COVID periods" submitted for the degree ofDoctor of Philosophy (PhD), specialty 8D10102 "Medicine".

Supervisor:
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Relevance of the study:

The COVID-19 pandemic has gone down in history as a global public health emergency, with the number of cases increasing sharply in a short time (Velavan & Meyer 2020). Coronavirus infection is caused by the SARS-CoV-2 virus, which is highly contagious and can be both asymptomatic and extremely severe, especially in the presence of a comorbid background (Siddiqu et al. 2020).The virus has demonstrated the ability to infect not only the respiratory system, but also other organs and systems, with approximately 2/3 of patients experiencing various neurological symptoms (Chou et al. 2021; Mao et al. 2020). In the early months of 2020, the SARS-CoV-2 virus was recognized as a potential neurotropic virus. According to scientists, in 2020, neurological disorders occurred in approximately 36.4% of patients with COVID-19 (Mao et al. 2020).

Central nervous system disorders include headache, dizziness, impaired consciousness, encephalopathy, acute symptomatic epileptic seizures, cerebrovascular disorders, encephalitis, and acute myelitis. Peripheral disorders include isolated cranial nerve dysfunction (anosmia and ageusia), Guillain-Barre syndrome, and myositis-like muscle damage (Dalakas M.C. 2020). Neuropathies and encephalopathies that occur in COVID-19 are serious complications with an as yet incompletely understood epidemiology, diagnostic criteria, and treatment approaches (Karami et al. 2023). Regardless of the direct or indirect effects of the virus, damage to the central nervous system (CNS) and peripheral nervous system (PNS) due to COVID-19 may become irreversible. To date, it is obvious that a population of patients has formed who have persistent neurological disorders.Their symptoms of CNS and PNS damage persist for more than 12 weeks after recovery from a viral infection and negatively affect their quality of life and health. This group of patients requires constant medical support by doctors of various specialties and medical and psychological rehabilitation, the measures of which have not yet been fully developed. Understanding the spectrum of these disorders and their pathogenesis is critical for developing treatment protocols and rehabilitation programs. The patients who suffered from COVID-19 suffered physically in the first place, as most of them suffered quite severely from the disease. However, along with this, patients also faced a number of psychological problems. Despite the fact that at the beginning of the pandemic, doctors focused on the physical health of patients, within a few months

after its onset it became clear that psychological problems could also be extremely dangerous for the health of patients (Ostryakova et al. 2021).

In the existing literature, there appears to be a significant variation in neurological disorders in the acute period from 20% to 70%, and time has shown that not all neurological disorders in the acute period remain permanent (Taherifard and Taherifard, 2020). In this regard, it has become relevant that neurological manifestations in the acute period and permanent neurological complications in the post- COVID period, as well as during the long-term outcome, require completely different approaches, both in diagnosis and in therapy with rehabilitation programs (Astin et al. 2023).

The spectrum, nature, and impact of neurological complications of COVID-19 on an individual's health and quality of life have not yet been fully studied. This is due to the relatively short period of catamnestic observation, the complex nature of pathology, and the limited number of scientific studies with a high level of evidence devoted to this problem. Since COVID-19 is a new disease, the number of publications about its association with neurological complications, both in the acute period and after it, is constantly increasing. To date, it remains open to discussion whether this infection will be associated with longer-term neurological consequences. A study of literary sources has shown that currently an urgent and important task is to present an analysis of the spectrum of neurological disorders in COVID-19 and in the long term, which was the rationale for conducting this study. Studying this topic will contribute to improving patient outcomes, optimizing medical care, and developing new approaches to treatment and rehabilitation.

Purpose of the study: Based on the analysis of neurological disorders of the acute period of COVID-19, to study the risk of developing persistent neurological disorders in the post-COVID period.

Objectives of the study:
1. To study the spectrum of neurological disorders in the acute period of COVID-19.
2. To conduct a comparative analysis of neurological disorders of the acute and post-COVID periods.
3. To study the risks of developing persistent neurological disorders in the post-COVID period

Scientific novelty of the study:
1. The frequency and spectrum of neurological disorders were studied, both in the acute period of COVID-19 and in the post-COVID period, with the identification of early markers of persistent neurological disorders.
2. Based on the predicate values of neurological disorders in the acute period of COVID-19, a step-by-step algorithm for predicting persistent neurological disorders has been developed.

Theoretical and practical significance: An algorithm for predicting persistent neurological disorders has been developed, which contributes to the timely identification and assessment of the risk of implementation in the long term.

The results of the study can serve as a basis for making additions to the clinical protocols for the diagnosis and treatment of headaches, and can be used in the development of methodological recommendations on headaches for neurologists.

The results of the dissertation work were introduced into the educational process of the Department of Neurology with a course in Psychiatry and Narcology of the NCJSC "WKMU named after Marat Ospanov", as well as into practical healthcare.

Main provisions submitted for defense

1. Neurological disorders in the acute period of COVID-19 are represented by lesions of the central and peripheral nervous system, the frequency of which was 42.8% (95%CI40.2-45.4%). Olfactory impairment prevailed- 73.5% (95%CI69.4-77.3%), taste impairment- 63.2% (95%CI58.8-67.4%) and headache-31.9% (95%CI27.8-36.2%). The relationship between the frequency and severity of clinical manifestations with the severity of COVID-19 was revealed in lesions of the central nervous system (stroke, acute encephalitis, acute symptomatic epileptic seizures, secondary headache) ($p<0.05$).

2. The incidence of neurological disorders in the post-COVID period decreased to 11.8% (95% CI 10.2-13.6), while the impaired sense of smell and taste fully recovered. Cognitive impairments sleep disorders, and depressive syndrome debuted during this period. Persistent neurological disorders were tension headache, depressive syndrome, and cognitive impairment.

The intensity of headache decreased from 5.49 ± 2.39 to 1.62 ± 0.98 and from 5.69 ± 3.24 to 2.39 ± 1.91 points on the VAS scale at II and III degrees ($p<0.001$), respectively.

The severity of depressive syndrome was mild in grade II and III (8.00 ± 0.0 and 9.24 ± 0.79 points on the HDRS scale, respectively), while in grade IV it remained severe (18.5 ± 0.57 points) ($p<0.05$).

The severity of cognitive impairment improved in grade III patients ($p=0.004$), while no improvement was achieved in grade IV ($p=0.096$). The incidence of neurological disorders in the post-COVID period decreased to 11.8% (95%CI10.2-13.6), while the impaired sense of smell and taste fully recovered. Cognitive impairments sleep disorders, and depressive syndrome debuted during this period. Persistent neurological disorders were tension headache, depressive syndrome, and cognitive impairment.

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The severity of cognitive impairment improved in grade III patients($p=0.004$), while no improvement was achieved in grade IV($p=0.096$).

3. Logistic regression analysis for persistent disorders showed: for cognitive impairments, OR 31.88 (95% CI: 22.52-43.25) with an age factor of 75-90 years and OR 49.19 (95% CI: 39.62-61.22) with a factor of IV degree COVID-19; for tension headache, OR 3.7 (95% CI: 1.7 – 7.9) with an age factor of 45-59 years and with a factor of III degree of COVID-19– the OR was 7.9 (95% CI: 3.7 – 16.8); for depressive syndrome with III degree, the OR was 22.5 (95% CI: 54.1 – 9.3).

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Approbation of the work

The main provisions of the dissertation were presented at an extended meeting of the Scientific Problem Commission of the West Kazakhstan Marat Ospanov Medical University.

The results of the study were reported on:

1. XVI International Conference "Distance Education in Medicine," February 19–20, 2021, Uzbekistan, Tashkent. Report: "The Spectrum of Neurological Disorders in COVID-19."

2. Scientific-Practical Conference "Current Issues in Neurology," March 24–25, 2021, Uzbekistan, Tashkent. Report: "Neurological Disorders in COVID-19."

3. Scientific-Practical Conference "Current Issues in Comorbid Neurology," April 21, 2021, Sibai Medical District of the Republic of Bashkortostan, Ufa. Report: "Characteristics of Headaches in Patients with COVID-19."

4. Scientific-Practical Conference with a Master Class "COVID-19 Today: A Multidisciplinary Perspective," May 26, 2021, Republic of Bashkortostan, Ufa. Report: "Rare Neurological Conditions Associated with COVID-19."

5. The Second International Scientific-Practical Virtual Conference in Modern Medicine "Women's Health and Reproductive Endocrinology: Prognosis, Achievements, and Challenges," July 30–31, 2021, Estonia-Tallinn, Azerbaijan-Estonia-Georgia-Kazakhstan-Turkey. Report: "Cerebrovascular Disorders in COVID-19."

6. Collection of scientific articles based on the materials of the VI International Scientific and Practical Conference of the Caspian Littoral States "Topical issues of Modern Medicine". Report: Peripheral neuropathy of the olfactory nerve in COVID-19 Caspian Bulletin of Medicine and Pharmacy, 2021, Volume 2, No. 2, p. 6-10.

7. Scientific and Practical Conference "Modern medicine: a new approach and relevant research" among the medical educational organizations of Kazakhstan, FSU and beyond, confined to the World Osteoporosis Day (WOD) conducted within the framework of NTP AR09563004 "Features of metabolism and the state of bone mineral density in adolescent girls with primary dysmenorrhea". Report: Assessment of cognitive function by MoCa scale in patients with COVID-19. Vol. 57, issue 2, Декабрь 2021, p. 39

8. International Interdisciplinary Teleconference of Neurologists and Orthopedists "Which Patient Can a Neurologist Help: Russian and International Data", January 26, 2022, Republic of Bashkortostan, Ufa. Report: "Mental Disorders in Patients with Coronavirus Infection: The Role of a Neurologist."

9. LXI International Scientific Conference of Young Scientists "Science: Yesterday, Today, Tomorrow," dedicated to the 65th anniversary of the West Kazakhstan Marat

Ospanov Medical University, April 27–28, 2022. Report: "Cranial Nerve Damage in Coronavirus Infection."

10. X Annual International Scientific-Practical Conference "Current Issues in Medicine" and "IV Satellite Forum on Public Health and Healthcare Policy," April 27–28, 2023, Baku, Azerbaijan. Report: "The Impact of COVID-19 on the Nervous System."

11. LXII International Scientific Conference of Young Scientists "Science: Yesterday, Today, Tomorrow," dedicated to the 65th anniversary of the Student Scientific Society of the West Kazakhstan Medical University after named Marat Ospanov, April 27, 2023. Report: "The Use of the Hamilton Hospital Scale in Patients with Coronavirus Infection."

Publications on the topic of the dissertation

7 scientific papers have been published based on the dissertation topic:

6 scientific papers in journals indexed in the Scopus database.

1. Possible mechanism of central nervous system targeting and neurological symptoms of the new coronavirus (COVID-19): literature review//M. Jumagaliyeva, D. Ayaganov, S. Saparbayev, N. Tuychibaeva, I.A. Abdelazim, Y. Kurmambayev, Z. Khamidullina, S. Yessenamanova//European Review for Medical and Pharmacological Sciences 2023 Vol. 27 №19, p. 9420-9428.

2. Relation between Guillain-Barré syndrome and COVID-19: Case-Series// Merey Bakytzhanovna Jumagaliyeva, Dinmukhamed Nurniyazovich Ayaganov, Ibrahim Anwar Abdelazim, Samat Sagatovich Saparbayev, Nodira Miratalievna Tuychibaeva, Yergen Jumashevich Kurmambayev//Journal of Medicine and Life2023 Vol. 16 №9, p. 9420-9428.

3. Acute cerebrovascular events and inflammatory markers associated with COVID-19: an observational study// Merey Bakytzhanovna Jumagaliyeva, Dinmukhamed Nurniyazovich Ayaganov, Ibrahim Anwar Abdelazim, Samat Sagatovich Saparbayev, Nodira Miratalievna Tuychibaeva, Yergen Jumashevich Kurmambayev//Journal of Medicine and Life2023 Vol. 16 №10, p.1482-1487.

4. Neurological aspects of COVID-19// Aliyeva M.B., Saparbayev S.S., Ayaganov D.N., Kurmangazin M.S., Tuychibaeva N.M. // Kazan Medical Journal 2021 Vol. 102 № 6, p.877-886.

5. A clinical case of co-occurring mental disorder and coronavirus infection// Jumagaliyeva M.B., Ayaganov D.N., Yuldashev V.L., Akhmadeeva L.R.// Bulletin of Siberian Medicine 2023 Vol. 22 №1, p. 170–173

6. Hypoxical encephalopathy of patients with COVID-19// Jumagaliyeva M.B., Ayaganov D.N., Saparbayev S.S., Tuychibaeva N.M.// Iranian Journal of War and Public Health. 2022 Vol. 14 №4,p.401-408

1 article in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Education and Science of the Republic of Kazakhstan:

1. M.B. Jumagaliyeva, D.N. Ayaganov, S.S. Saparbayev, A.O. Umurzakova. A change in the mental status of a patient against the background of a new coronavirus infection (clinical case). Pharmacy of Kazakhstan. 2022 Vol. 3 № 242, p. 65-70

4 abstracts - in collections of International scientific and practical conferences
3 acts of implementation:
In practical healthcare:
     - Acts of implementation No. 200 dated December 13, 2021, "Using the NIHSS scale in patients with COVID-19 to assess neurological status and diagnose stroke";
     - Acts of implementation No. 201 dated December 13, 2021, "Anosmia and ageusia as potential symptoms of COVID-19";
In the educational process:
     - Acts of implementation No. 199 dated December 23, 2021, "Neurological disorders in COVID-19";

Personal contribution of the author

The author conducted a thorough analysis of scientific sources related to the topic of the dissertation. All parts of this research, including the goals, objectives, research program, processing of statistical data, interpretation of the results, conclusions and practical recommendations, were completed by the author independently.

Materials and methods of the study:

A prospective cohort study was conducted from February 1 to April 30, 2021. The work was performed in Aktobe at the clinical bases of the NCJSC "West Kazakhstan Medical University named after Marat Ospanov": Aktobe regional Phthisiopulmonological Center, SUC "Regional Clinical Infectious Diseases Hospital", Aktobe Regional Mental Health Center, as well as a specialized treatment and preventive enterprise.

Continuous sequential sampling was used. 2708 patients were hospitalized with a diagnosis of Coronavirus infection, of which 1,415 patients were PCR-positive. Symptoms of neurological disorders were detected in 606 patients, of whom 495 patients signed an informed consent to participate in the study. Thus, the final sample consisted of 495 patients with grades II, III and IV of COVID-19 severity (patients with grade I severity were not admitted to hospitals).

During the initial examination, an objective neurological examination was performed using specialized scales and questionnaires. During the visit, after 3 months (early post- COVID period) and 6 months (late post-COVID period), the neurological status was assessed using the same scales and questionnaires.

Combined estimates of epidemiological studies of neurological complications in COVID-19, according to literature data, range from 8% to 36.4% [6]. According to the statistical report, 616,565 adults live in Aktobe region (stat.gov.kz). Using the statistical program "EpiInfoTM" (official website http://www.cdc.gov/epiinfo /) and calculating in the "StatCalc" section a representative sample with an alpha error correction of 5% and a beta threshold of 20% (80% power), the sample size should be 404 patients. Our sample according to the inclusion criteria was 495.

The severity of COVID-19 is classified according to the clinical protocol for the diagnosis and treatment of coronavirus infection in adults, approved by the Joint Commission on Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan dated July 15, 2020, Protocol No. 106.

The age of the patients was classified according to WHO: 18-44 years – young, 45-59 - middle, 60-74 – elderly, 75-90 – senile.

The clinical study of patients included a scale assessment: The Glasgow Coma Severity Scale was used to assess the level of impaired consciousness and the degree of coma. The NIHSS scale was used to determine the severity of stroke at the National Institutes of Health in the United States. The visual analog scale VAS was used to measure the intensity of the headache. The Montreal Cognitive Function Assessment Scale (MoCA) was used to assess the degree of cognitive disorders. The HDRS scale was used to determine the level of depression and anxiety. The ILAE 2017 classification was used to identify epileptic seizures.

The work follows the principles of the Helsinki Declaration of the World Medical Association, 1964, updated in October 2013 at the 64th General Assembly of the World Medical Association, Fortaleza, Brazil.

The dissertation research was examined by the local Bioethics Commission at the Marat Ospanov National State Medical University of Aktobe dated January 21, 2021, Protocol No. 1.

Inclusion criteria:
- age from 18 to 90 years;
- positive PCR test for SARS-CoV-2 RNA;
- the presence of a neurological disorder

Exclusion criteria:
- under 18 years of age and over 90 years of age;
- negative result of the PCR test;
- vulnerable group of patients (decompensated for somatic diseases, pregnant);
- repeated case of COVID-19;
- patients with neurological disorders unrelated to COVID-19.

Taking into account the inclusion and exclusion criteria, according to the set goals and objectives, a prospective cohort study was conducted.

Objective 1: **To study the spectrum of neurological disorders in the acute period of COVID-19**.

A prospective study was conducted. In the acute period of COVID-19, all 1,415 patients were examined for neurological disorders. Neurological disorders were reported in 495 patients. All patients were ranked by severity of COVID-19 (II, III, IV), by age, according to the WHO classification (4 categories). The relationship between the age of patients and the severity of COVID-19 was determined. The diagnosed disorders are divided into CNS and PNS lesions. The frequency of neurological disorders was studied across the entire spectrum of disorders, as well as by severity of COVID-19.

Objective 2: **To conduct a comparative analysis of neurological disorders of the acute and post-COVID-19 periods.**

In the post-COVID period (after 3 and 6 months), a neurological examination was repeated. A comparative assessment of the dynamics of the incidence of neurological disorders in terms of the severity of COVID-19, in comparison with the acute period, was carried out. Taking into account recovered patients, fatal cases, and newly infected COVID-19, the sample consisted of 459 and 433 patients,

respectively, after 3 and 6 months. Based on a comparative analysis, the following persistent neurological disorders have been identified: neurological deficits due to stroke, encephalitis, and GBS, depressive syndrome, epilepsy, cognitive impairment, and headache.

Objective 3: **To study the risks of developing persistent neurological disorders in the post- COVID period.**

The persistent neurological disorders were cognitive impairment, tension headache, and depressive syndrome, for each of which a logistic regression analysis was performed to predict the persistence of neurological disorders. A prognostic model has been developed to determine the likelihood of persistent neurological disorders after 6 months in patients who have suffered from COVID-19, depending on the factors for which a logistic regression analysis has been performed. The influence of factors such as gender, age, and severity of COVID-19 was studied.

Statistical methods of the study: The primary descriptive analysis was conducted to study the characteristics and distribution of variables.

Descriptive statistics were used to analyze demographic factors and ordinal features. The relationship between the severity of COVID-19 and the age of patients was analyzed using a nonparametric Spearman rank correlation. The average value and standard deviation in the form of "M±S" were used to describe the quantitative variables. To describe the spectrum of neurological disorders, the nonparametric Wilcoxon test was used at each stage of the assessment to assess the differences between two dependent samples measured using an ordinal scale. The Pearson Chi-square method was used to determine the statistical significance of the differences between the groups for binary and nominal scales. The McNemar's criterion was used to compare the frequency of distribution of neurological disorders in dependent groups, in the acute and post-COVID periods. To study the dynamics (to identify differences between groups) of neurological disorders depending on the severity of COVID-19 in the acute and post-COVID periods, ANOVA analysis of variance was used.

A logistic regression analysis was used to predict and identify the risk of headaches, depression, and cognitive impairment in the long term, depending on their characteristics in the acute period. Prior to the analysis of logistic regression, the pseudorandomization method was used for headaches in order to eliminate systematic differences between the compared groups and ensure maximum comparability of the main and reference groups according to the available confounders. The level of statistical significance was fixed at 0.05.

Statistical data processing was carried out using IBM SPSS Statistics application software packages, version 25 (SPSS Inc., Chicago, IL, USA), and GraphPad software (Version 9.5.1, San Diego, California, USA) was used for graphical representation.

Main results of the study

Characteristics of neurological disorders in the acute period of COVID-19.

Neurological manifestations of COVID-19 are represented by disorders of the central and peripheral nervous system in 495 (35%) patients, there were 1077 signs in total (1 patient had several neurological disorders simultaneously). Neurological

disorders in the acute period of COVID-19 are represented by lesions of the central and peripheral nervous system, the frequency of which was 42.8% (95% CI 40.2-45.4%). Olfactory impairment prevailed - 73.5% (95% CI 69.4-77.3%), taste impairment - 63.2% (95% CI 58.8-67.4%) and headache - 31.9% (95% CI 27.8-36.2%). The relationship of the frequency of neurological disorders with the severity of COVID-19 (II, III, IV degrees) was revealed in stroke (4,9%, 11,3%, 43,3%); acute encephalitis (1,5%, 4,2%, 13,3%); acute symptomatic epileptic seizures (1,9%, 5,4%, 18,3%), dysmetabolic encephalopathy (5,2%, 9,5%, 13,3%) and secondary headaches (23,2%, 44,6%, 35%), accordingly (p<0.05), and in case of headache, there is a relationship with its intensity (according to the VAS scale): in grade II and III patients, it was listed as "strong" (4.20±2.35 and 5.86±2.58 points), in grade IV patients as "strongest" (7.23±1.75 points).

Comparative characteristics of neurological disorders of the early and late post-COVID periods with the acute period.

The incidence of neurological disorders in the post-COVID period decreased to 11.8% (95% CI 10.2-13.6), while the impaired sense of smell and taste fully recovered. Cognitive impairments sleep disorders, and depressive syndrome debuted during this period. Persistent neurological disorders were tension headache, depressive syndrome, and cognitive impairment. The intensity of headache decreased from 5.49±2.39 to 1.62±0.98 and from 5.69±3.24 to 2.39±1.91 points on the VAS scale at II and III degrees (p<0.001), respectively. The severity of depressive syndrome in dynamics was mild at grade II and III (8.00±0.0 and 9.24±0.79 points on the HDRS scale, respectively), while at grade IV it remained severe (18.5±0.57 points) (p<0.05). The severity of cognitive impairment improved dynamically in grade III patients (p=0.004), while no improvement was achieved in grade IV patients (p=0.096).

To study the risks of developing persistent neurological disorders in the post-COVID period.

Persistent neurological disorders were cognitive impairment, tension headache, and depressive syndrome, for each of which a logistic regression analysis was performed to predict the persistence of neurological disorders. We have developed a prognostic model that includes certain factors (gender, age, and severity of COVID-19) to determine the likelihood of long-term neurological consequences in the post-COVID period. Significant risk factors for cognitive impairment are: grade III increases the odds by 26.29 times (95% CI: 11.41-37.49), and grade IV – by 49.19 times (95% CI: 39.62-61.22); age 60-74 years – by 2.62 times (95% CI: 1.22-5.61) and age 75-90 years – 31.88 times (95% CI: 22.52-43.25). Risk factors for headaches are: grade III increases the chances by 7.9 times (95% CI: 3.7 – 16.8), IV – by 3.5 times (95% CI: 1.5 – 7.9); age 45-59 years – by 3.7 times (95% CI: 1.7 – 7.9), 60-74 years – by 4.2 times (95% CI: 0.6 – 7.6) and 75-90 years – 7.6 times (95% CI: 0.4 – 14.9). The risk factors for depressive syndrome were: grade III increases the risk by 22.5 times (95% CI: 54.1 – 9.3), grade IV – by 4.9 times (95% CI: 18.2 – 1.3).

Conclusions:

1. The incidence of neurological disorders in the acute period of COVID-19 was 42.8% (95% CI 40.2-45.4%) and represented by lesions of the central and peripheral nervous system. Olfactory impairment prevailed - 73.5% (95% CI 69.4-77.3%), taste impairment - 63.2% (95% CI 58.8-67.4%) and headache - 31.9% (95% CI 27.8-36.2%). The relationship between the frequency and severity of clinical manifestations with the severity of COVID-19 ($p<0.05$) was revealed.

2. The incidence of neurological disorders in the post-COVID period decreased to 11.8% (95% CI 10.2-13.6), while the impaired sense of smell and taste fully recovered. During this period, cognitive impairments sleep disorders, and depressive syndrome manifested for the first time. Persistent neurological disorders were tension headache, the intensity of which decreased only at grade II and III ($p<0.001$), at grade IV depressive syndrome ($p<0.05$) and cognitive impairment remained severe.

3. In the post-COVID period, the risk of cognitive impairment at grade IV is OR 49.19 (95% CI: 39.62-61.22), depressive syndrome at grade III is OR 22.5 (95% CI: 54.1–9.3), tension headache at grade III is OR 3.7 (95% CI: 1.7 – 7.9) and at the age of 45-59 years – OR 7.9 (95% CI: 3.7 – 16.8).