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PREDICTING THE DEVELOPMENT OF COGNITIVE IMPAIRMENT IN PATIENTS AFTER COVID-19 INFECTION

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The study focused on predicting the development of cognitive impairment in patients following COVID-19. The study involved 100 patients, 69 in the main group and 31 in the control group. In terms of gender composition, men predominated – 60 people. According to the results of a comprehensive clinical and neurological examination, as well as neuropsychological examination, which considers quality of life indicators and laboratory examination, specifically the level of phosphorylated neurofilament, this factor is identified as a predictor of the development of the neurodegenerative process. Patients in the main group (n=69) were divided into 2 subgroups based on the level of neurofilament: the NfL-N subgroup with a concentration not exceeding the norm and the NfL-P subgroup with a concentration above the norm. A predictive model for the development of cognitive impairment in patients with COVID-19 has been developed to improve early diagnosis of neurodegenerative diseases.

Key words: prediction, cognitive impairment, depression, anxiety, COVID-19, neurofilaments.

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ПРОГНОЗУВАННЯ РОЗВИТКУ КОГНІТИВНИХ ПОРУШЕНЬ У ПАЦІЄНТІВ ПІСЛЯ ПЕРЕНЕСЕНОЇ ІНФЕКЦІЇ COVID-19

Дана стаття присвячена прогнозуванню розвитку когнітивних порушень у пацієнтів після перенесеного захворювання COVID-19. В дослідження залучено 100 пацієнтів, 69 осіб основної групи та 31 особа контрольна група. За гендерним складом переважали чоловіки – 60 осіб. За результатами комплексного клініко-неврологічного обстеження, нейропсихологічного обстеження з урахуванням показників якості життя, проведення лабораторного обстеження, а саме рівня фосфорильованого нейрофіламента як предиктора розвитку нейродегенеративного процесу. У подальшому пацієнтів основної групи (n=69) було розділено на 2 підгрупи в залежності від рівня нейрофіламенту: підгрупа NfL-N з концентрацією, що не перевищую норму, та підгрупа NfL-P з концентрацією, що вище норми. Була розроблена прогностична модель розвитку когнітивних порушень у пацієнтів, що перенесли COVID-19 для удосконалення ранньої діагностики нейродегенеративних захворювань.

Ключові слова: прогнозування, когнітивні порушення, депресія, тривога, COVID-19, нейрофіламенти.

The work is a fragment of the research project "Clinical, pathogenetic and prognostic markers of nervous system disorders and optimization of diagnostic and treatment algorithms", state registration No. 0122U201970.

The COVID-19 pandemic has become a problem for society that requires further detailed study, primarily regarding early diagnosis of complications after the disease to prevent the development of long COVID syndrome. Coronavirus disease is a systemic pathology that affects all organs and systems of the body at different stages of the disease. From the side of the nervous system, this can manifest itself in

various symptoms, the first and most important of which are anosmia, headache, dizziness, impaired consciousness, seizures, insomnia, impaired memory, attention, concentration, general weakness, decreased performance, and anxiety. The development of neurological diseases after COVID-19 infection is most often manifested by acute cerebrovascular pathology, which includes cerebral strokes, venous sinus thrombosis, meningoencephalitis [5], hemorrhage into the brain substance and ventricular system [8]. In addition to affecting the central nervous system, COVID-19 also damages the peripheral nervous system, which manifests itself in the form of mononeuropathies, polyneuropathies, and radiculopathies. One of how the peripheral nervous system is affected, with subsequent possible penetration of the infection into the brain, is through damage to the olfactory nerves [4].

One of the main consequences of suffering a coronavirus disease is the development of anxiety and depression, which does not depend on the severity of the disease [10, 15].

Post-COVID syndrome is a multisystem disease that occurs after a mild or asymptomatic course of COVID-19 and is accompanied by long-term respiratory, cardiovascular, and neuropsychiatric consequences that last more than 12 weeks [9].

In modern medical literature, markers of nervous system damage are increasingly found, one of which is the biomarker of phosphorylated neurofilament (Nf) as a predictor of the development of neurodegenerative diseases, which requires more detailed study. When neurons are damaged, the concentration of Nf increases in cerebrospinal fluid and blood serum. This naturally allows us to study this indicator as a potential biomarker for developing various neurological diseases [12]. Neurofilaments are an essential part of neurocytoskeletal structures in the bodies and projections of central and peripheral nervous system neurons [7].

Therefore, to improve timely and early diagnosis and high-quality prognostic assessment of neurodegenerative diseases after coronavirus, there is a need to study phosphorylated neurofilament as one of the primary markers of axonal damage [6].

The increase in neurofilament concentration in the cerebrospinal fluid and/or blood is interdependent with the degree of axonal damage in various neurological disorders, primarily inflammatory, neurodegenerative, traumatic, and cerebrovascular diseases [11, 12]. For early diagnosis and prediction of the development of active neurodegeneration, the level of neurofilament in blood plasma can be considered a reliable marker in the future.

Neurological complications after COVID-19, namely cognitive impairment, require further study in the future by doctors of all specialties, namely the need to improve early diagnosis of neurodegenerative diseases. This will allow for detailed prediction of cognitive impairment.

The purpose of the study was to develop a predictive model for the development of cognitive impairment in patients following COVID-19 infection within 6 months, aiming to improve the early diagnosis of neurodegenerative diseases.

Materials and methods. The study was conducted on the basis of the Municipal Enterprise “Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov” of the Dnipropetrovsk Regional Council, the Municipal Non-Profit Enterprise “City Clinical Hospital No. 21 named after Prof. Ye.G. Popkova” of the Dnipropetrovsk City Council from 2021–2023. All studies conducted within the framework of this work were performed by the principles of the World Medical Association's Declaration of Helsinki, “Ethical Principles for Medical Research Involving Human Subjects”, and the “Universal Declaration on Bioethics and Human Rights (UNESCO)”. Written informed consent was obtained from all patients participating in the study.

The study included 100 patients divided into two groups: main and control. The median age of the main group was 49 (37; 56) years, and the control group was 42 (37; 53) years. In terms of gender composition, men predominated – 60 people, 40 people were women. The main group included patients with a confirmed diagnosis of COVID-19 and who received inpatient or outpatient treatment.

All study participants underwent a clinical and neurological examination, cognitive changes were assessed using the MoCA scale, the development of depression using the Beck questionnaire, indicators of situational and personal anxiety using the Spielberger scale, and their relationship with the level of neurofilament was studied. Patients in the main group (n=69) were divided into 2 subgroups depending on the level of neurofilament: the NfL-N subgroup with a concentration not exceeding the norm and the NfL-P subgroup with a concentration above the norm. Patients were examined twice at the onset of the disease and after 6 months.

The research results were processed using the STATISTICA package (StatSoft Inc., ver.6.1, serial number AGAR909E415822FA). The visualization of the obtained data was carried out using Microsoft

Office, MedCalc, and STATISTICA packages. ROC analysis and construction of ROC curves were performed in the MedCalc software package (www.medcalc.org, trial version 20.009).

Since the distribution of most data differed from normal, continuous variables are presented as median (Me) with the first and third quartiles (25; 75). Categorical data are presented as an absolute number of cases (n) and percentage within the study group (%). The percentage was reported with a 95 % confidence interval (CI) [1, 2, 13].

To assess the normality of the distribution of quantitative indicators, the Shapiro-Wilk test (for $n < 60$) and the Kolmogorov-Smirnov test with the Lilliefors correction (for $n > 60$) were used. The equality of variances was evaluated using the Fisher test.

Correlation analysis using the Spearman coefficient (r) was employed to assess the relationship between features. In the case of a positive result, the relationship was assessed as direct (an increase in one indicator is associated with an increase in another) and as inverse in the case of a negative result. To assess the relationship between nominal features, the association coefficient (φ) was calculated [1].

To determine the statistical significance of differences between independent groups, the Mann-Whitney U test was used for quantitative variables, while the Pearson χ^2 test (with Yates' correction) or Fisher's exact test was used for nominal variables. The statistical significance of differences between dependent groups for quantitative data was established using the Wilcoxon T-test, and for nominal data, the McNemar test (with Edwards's correction to improve accuracy in samples with rare events) [1, 13].

The predictive ability of the constructed model was assessed using ROC analysis to determine the area under the ROC curve with 95 % CI and the Somers' D correlation coefficient.

ROC analysis (Receiver Operating Characteristic curve analysis) was used to assess the discriminatory ability of the indicators. It included constructing and analyzing operating characteristic curves and calculating the area under the ROC curve (AUC) with its 95 % CI. Sensitivity (Se) and specificity (Sp) indicators were determined.

Results of the study and their discussion. According to the study results, 6 months after the onset of the disease, cognitive functions had not recovered in some patients, and the MoCA score did not reach the expected level of 26 points. This effect was more pronounced in individuals from the main group (n=69).

To further analyze factors that could affect cognitive function after COVID-19, patients were divided into two groups: Group 1 consisted of patients with cognitive impairment, as determined by the MoCA, and Group 2 consisted of patients with no cognitive impairment, as determined by the MoCA.

It was also found that the time factor does not significantly affect the cognitive functions of patients who have had COVID-19. Cognitive impairments in individuals with the disease remained unchanged after 6 months of observation, and patients who did not have impairments at the onset of the disease were not detected after six months. According to MoCA, the presence and persistence of cognitive impairment after COVID-19 requires the search for factors that can predict an insufficient level of cognitive functions.

When comparing groups based on the presence of intellectual disabilities after a 6-month follow-up, statistically significant differences were found between all indicators analyzed during the study (Table 1).

Table 1

Psychometric indicators in comparison groups

Indicator	MoCA<25 p. (n=52)	MOCA≥25 p. (n=48)	p*
Luria test, word count	3 (3; 4)	8 (6.5; 9.0)	<0.01
Schulte test, seconds	157 (139; 173)	118 (112; 137)	<0.01
Beck's Depression Inventory, points	19 (15.5; 21)	6 (3; 11)	<0.01
Situational anxiety, points	56 (45.5; 61)	24 (21; 40)	<0.01
Personal anxiety, points	47.5 (41; 53.5)	26 (23.5; 35)	<0.01
Mental component of QoL, points	46.9 (44.2; 49.9)	49.8 (47.1; 51.3)	<0.01
Physical component of QoL, points	37.0 (33.8; 40.0)	49.4 (39.9; 52.0)	<0.01

Note. Data are presented as Me (25; 75). * – difference between groups according to the Mann-Whitney test.

In the next step, the indicators on which the groups significantly differed were included in the correlation analysis (Fig. 1).

When analyzing categorical variables in groups, significant differences were found in the indicators of depression, personal and situational anxiety, and the result obtained by the Luria test.

The results of the search for associations between the categorical variable MoCA and indicators are shown in Fig. 2.

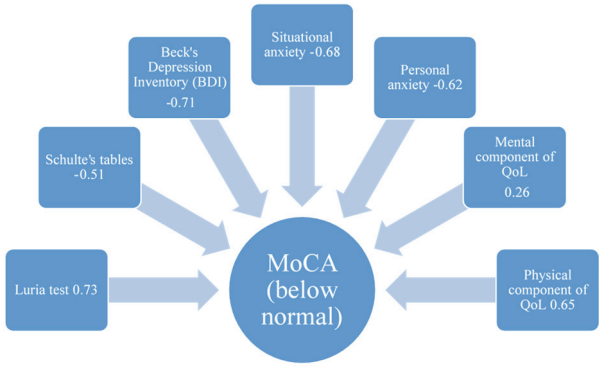

Fig. 1. Correlations between the binary variable of cognitive function and continuous indicators of psychoemotional characteristics of patients. Note. The numerical symbols indicate the correlation (r_s).

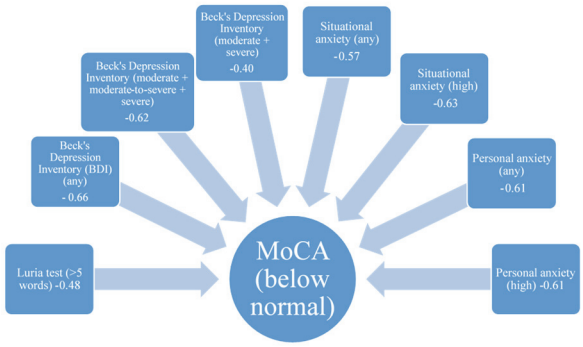

Fig. 2 Relationship between binary variables of cognitive function and psychoemotional indicators of patients. Note. The numerical symbols show the associative relationship (φ), and the characteristic, coded as "1", is given in parentheses.

The indicators measured at the initial examination that differed between the groups with or without an adequate cognitive level, as determined by the MoCA at 6 months of follow-up, along with categorical variables, were entered into a univariate logistic analysis. The predictive power of the obtained results, along with an assessment of the quality of the predictive models, is presented in Table 2 (for continuous variables).

Table 2

Univariate logit analysis of predictors of cognitive impairment (continuous variables)

Predictor	B	P	OR (95 % CI)	AUC (95 % CI)	Se	Sp	Criterion
MoCA	-1.42	<0.001	0.24 (0.13–0.44)	0.94 (0.87–0.98)	86.5	91.7	≤25
Luria Test	-0.82	<0.001	0.44 (0.33–0.58)	0.92 (0.84–0.96)	75.0	91.7	≤4
Beck's Depression Inventory	0.32	<0.001	1.38 (1.23–1.55)	0.91 (0.83–0.96)	86.5	83.3	>11
Situational anxiety	0.13	<0.001	1.13 (1.09–1.19)	0.89 (0.82–0.95)	78.8	85.4	>42
Personal anxiety	0.14	<0.001	1.15 (1.09–1.21)	0.86 (0.77–0.92)	76.9	87.5	>38
Mental component of QoL	-0.15	0.01	0.86 (0.76–0.97)	0.65 (0.55–0.75)	71.2	58.3	≤49.49
Physical component of QoL	-0.22	<0.001	0.80 (0.74–0.87)	0.87 (0.79–0.93)	86.5	83.3	≤39.12

Based on the results of the univariate analyses of cognitive function predictors (continuous variables, categorical variables), the result of the analysis of heavy subunits of phosphorylated neurofilament as a predictor of cognitive impairment after 6 months was included in the study to build a multiple logistic model that would predict the development of cognitive impairment in a patient 6 months after COVID-19. Based on the study's results, several comparable prediction models were obtained.

The most optimal model includes a binary indicator of exceeding the NfL norm, a binary indicator of situational anxiety, and an indicator based on Schulte tables in points.

Further testing included determining the Hosmer–Lemeshow test, which was 9.326 (p=0.32), and using the maximum likelihood method, which revealed $\chi 2$=51.173, df=3, (p<0.0001). The results obtained indicate a correspondence between the data obtained in our study and the logistic model.

The resulting model had very good predictive ability as assessed by the predictive accuracy of the logistic regression equation using the ROC curve and area under the curve analysis. The AUC of the constructed model was 0.88 (95 % CI 0.80–0.93), p<0.0001, indicating its very good predictive ability. Thus, if, according to the constructed model, we obtain a result greater than 0.608, then the patient should be classified as a cohort with a good prognosis regarding cognitive functions after 6 months.

The next step of our study was to compare the accuracy of predicting cognitive impairment in patients 6 months after COVID-19 using the complex model we developed (multiple logistic regression) and separate models built for each of the factors included as components of the developed model (univariate models) using the ROC analysis method.

The results of the analysis showed that the complex model we developed significantly better predicts cognitive impairment in the separated period than any individual factor, and this difference is statistically significant.

The combination of indicators, including high levels of phosphorylated neurofilament heavy subunits, situational anxiety, and the severity of attention, according to the Schulte table, increases the likelihood of cognitive impairment 6 months after COVID-19 by 27.98 times.

The clinical, paraclinical, and psychometric factors identified in the study that affect the cognitive functions of patients with COVID-19 enabled the development of logistic models for predicting the decline in cognitive processes 6 months after COVID-19. The predictors included a high level of heavy subunits of phosphorylated neurofilament, situational and personal anxiety, the severity of attention deficit disorder according to Schulte tables, and indicators of the physical and mental components of quality of life.

According to the study results, 6 months after the onset of the disease, cognitive functions had not recovered in some patients, and the MoCA score did not reach the expected level of 26 points. It has been established that the time factor does not significantly affect the cognitive functions of patients with coronavirus disease. Cognitive impairments in individuals with the disease remained unchanged after 6 months of observation, and patients who did not exhibit impairments at the disease's onset did not develop them after 6 months. The indicators measured at the initial examination that differed between the groups with or without an adequate cognitive level, as determined by the MoCA at 6 months of follow-up, along with categorical variables, were entered into a univariate logistic analysis. When analyzing categorical variables in groups, significant differences were found in the indicators of depression, personal and situational anxiety, and the result obtained by the Luria test. Based on the results of the univariate analyses of cognitive function predictors (continuous variables, categorical variables), the result of the analysis of heavy subunits of phosphorylated neurofilament as a predictor of cognitive impairment after 6 months was included in the study to build a multiple logistic model that would predict the development of cognitive impairment in a patient 6 months after COVID-19. Based on the study's results, several comparable prediction models were obtained.

The most optimal model includes a binary indicator of exceeding the NfL norm, a binary indicator of situational anxiety, and an indicator based on Schulte tables in points.

Further testing included determining the Hosmer–Lemeshow test, which was 9.326 ($p=0.32$), and using the maximum likelihood method, which revealed $\chi 2=51.173$, $df=3$, $p<0.0001$). The results obtained indicate a correspondence between the data obtained in the study and the logistic model.

We compared the accuracy of predicting cognitive impairment in patients 6 months after COVID-19 using the complex model we developed (multiple logistic regression) and separate models built for each of the factors included as components of the developed model (univariate models) using the ROC analysis method. The results of the analysis showed that the complex model we developed significantly better predicts cognitive impairment in the separated period than any individual factor, and this difference is statistically significant.

Conclusions

1. The main prognostic factors for the development of cognitive impairment after COVID-19 were the results of the attention study using Schulte tables, the presence of situational anxiety, and the presence of high (above normal) levels of phosphorylated neurofilament heavy subunits.

2. According to the results of the obtained logistic prognostic model, the likelihood of cognitive disorders increases with the presence of attention disorders (according to Schulte tables), situational anxiety during the disease, and pathological levels of phosphorylated neurofilament heavy subunits.

3. The resulting logistic model exhibits very good predictive ability, with a coefficient of 0.877 (95 % CI 0.796–0.934), $p < 0.0001$. ROC analysis for the obtained logistic model established sensitivity – Se= 82.7 and specificity – Sp 89.6 with an optimal cutoff point >0.608. If all predictors are present, the chances of having cognitive impairment 6 months after COVID-19 increase by 27.98 times.

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ELDERLY PEOPLE WITH DIFFERENT TYPES OF NUTRITIONAL BEHAVIOR HEALTH STATUS AND QUALITY OF LIFE

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The purpose of the study was to assess the distribution of nutritional behavior types in different age groups of elderly people and their health status and quality of life. The research was conducted on the basis of 4 city polyclinics (patients, guests), 4 schools (parents) and 14 different companies and departments (employees) of Baku city. The types and social and hygienic aspects of the formation of feeding behavior were determined by a blind survey using the international DEBQ questionnaire. Quality of life was determined by the SF–36 international questionnaire. In total, the health of elderly people can be assessed as unsatisfactory according to the survey. Almost all types of nutritional behavior did not exceed 0.52 points, which corresponds to a low assessment of self-health. Health and quality of life indicators were lower for all types of nutritional behavior, only in mixed nutritional behavior type their indicators were more positive.

Key words: elderly people, quality of life, health status, eating behavior.

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РІЗНІ ТИПИ ХАРЧОВОЇ ПОВЕДІНКИ, СТАН ЗДОРОВ'Я І ЯКІСТЬ ЖИТТЯ У ЛІТНІХ ПАЦІЄНТІВ

Метою дослідження була оцінка розподілу типів харчової поведінки у різних вікових групах людей похилого віку, стану їх здоров'я та якості життя. Дослідження проводилося на базі 4 міських поліклінік (пацієнти, відвідувачі), 4 шкіл (батьки) та 14 різних підприємств та відомств (співробітники) міста Баку. Типи та соціально-гігієнічні аспекти формування харчової поведінки визначалися методом сліпого опитування з використанням міжнародного опитувальника DEBQ. Якість життя визначалася за міжнародним опитувальником SF-36. Загалом за результатами опитування здоров'я людей похилого віку можна оцінити як незадовільне. Практично всі типи харчової поведінки за опитувальником не перевищували 0,52 бали, що відповідає низькій оцінці власного здоров'я. Показники здоров'я та якості життя були нижчими за всіма типами харчової поведінки, тільки при змішаному типі показники були більш позитивними.

Ключові слова: люди похилого віку, якість життя, стан здоров'я, харчова поведінка.

One of the most urgent demographic problems worldwide is the ongoing population aging. According to the United Nations, the share of people over 65 years old has increased by 9 %, and in 2025, the number of people over 65 years old in the world will exceed 800 million, which will make up 10 % of the population. In 2050, this share may reach 16 %. All the mentioned shows once again that the number of the population belonging to the ≥65 age group will increase at a great pace compared to other population