ORIGINAL ARTICLE

COGNITIVE IMPAIRMENT IN PATIENTS HOSPITALIZED WITH COVID-19 PNEUMONIA: CORRELATION WITH DEMOGRAPHIC, CLINICAL AND EMOTIONAL PROFILE

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ABSTRACT

The aim: To study the structure of cognitive impairment in patients who were hospitalized with moderate to severe COVID-19 pneumonia. Investigate the correlation with demographic, biochemical parameters, as well as the emotional state of the patient.

Materials and methods: Cognitive functions were assessed using the MOCA test. PHQ-9 depression and GAD-7 anxiety questionnaires were used to study psychopathological symptoms. Demographic, clinical and laboratory data were extracted from medical records

Results: Cognitive performance is impaired in 94% of patients with COVID-19. This allows to suggest that COVID-19 has a serious impact on cognition, especially in elder people. Among different domains only visuospatial and executive functioning, abstract thinking, attention and delayed recall were severely impaired, while other domains stayed relatively intact. Patients after COVID-19 also tend to have a mild depressive and anxiety state. Anxiety levels were higher than depressive levels, but not connected to cognitive functioning. Also, there was seen a positive correlation between anxiety and pO2 and negative between anxiety and comorbid cardiac pathology. However, this requires further studies to reveal. Another interesting finding was non-linear relationship between cognitive performance and depression, that allows to suggest rapidly evolving depressive mood in persons with severe cognitive impairment after COVID-19. Cognitive and emotional state of patients after COVID-19 was also highly connected with working status.

Conclusion: Significant cognitive impairment was presented in almost all patients with COVID-19**.** There was a selective impairment in domains of visuospatial/ executive functioning, abstract thinking, attention and delayed recall.

Conclusions: Significant cognitive impairment was presented in almost all patients with COVID-19. There was a selective impairment in domains of visuospatial/ executive functioning, abstract thinking, attention and delayed recall.

KEY WORDS: Covid-19, Cognitive impairment, Inpatients, Depression, Anxiety

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INTRODUCTION

Since the end of 2019, we have all been living under the influence of the severe viral COVID-19 pandemic, which primarily affects the respiratory system, causing bilateral pneumonia, but is increasingly recognized as a systemic disease that directly affects the central nervous system (CNS). 36.4–82.3% of hospitalized Covid-19 patients worldwide had neurological manifestations of varying severity [1]. Many patients recovering from COVID-19 also have psychiatric, neurological and cognitive problems in the next 3-6 months [2,3]. Moreover, these problems occur in approximately 85% of severally ill patients with COVID-19 who have been hospitalized [4] and persist long after recovery from the primary infection and adversely affect the subsequent quality of life [5].

Reports have also been shown that depression, anxiety, insomnia and post-traumatic stress disorder are common effects of COVID-19 on the human psyche [6-8].

The study performed by Miners S et al. (2021), revealed that almost 2/3 of hospitalized COVID-19 patients had complications in the form of ischemic, hemorrhagic and inflammatory lesions of the CNS, and most ischemic lesions of the CNS vascular system were mediated by direct or secondary exposure to the virus [9]. Primary brain damage can be provoked by the virus, possibly through the olfactory nerve, which directly causes encephalitis [10]. Secondary exposure to the virus means coagulopathies with a prothrombotic state and an inflammatory «cytokine storm». [11].

Elderly people are vulnerable to severe forms of COVID-19 due to factors associated with the increased prevalence of comorbid somatic diseases such as hypertension, coronary heart disease, diabetes, obesity, and general aging factors, making them more vulnerable to possible long-term mental and cognitive disorders [12,13].

In one American study, 50 hospitalized patients with COVID-19 who were admitted to the hospital had neurological symptoms and 24 % complained on short-term memory loss [14]. In a sample of 71 hospitalized patients with COVID-19, 42% showed confused consciousness. These patients had lower cognitive performance after 4 weeks of discharge, although comparisons between groups

Table I. Clinical characteristics of study population.

Clinical characteristic	Total (n = 100)	Male (n = 48)	Female (n = 52)	p
pO2	92.79 ± 4.98	93.56 ± 3.12	92.27 ± 5.90	0.321
Hb	142.23 ± 11.34	147.16 ± 10.38	139.00 ± 10.89	0.004
RBC	4.48 ± 0.33	4.42 ± 0.36	4.58 ± 0.31	0.069
HCT	41.08 ± 3.19	42.42 ± 3.12	40.17 ± 2.96	0.005
ESR	26.77 ± 13.37	25.68 ± 14.53	27.50 ± 12.71	0.601
PLT	219.87 ± 90.62	211.28 ± 84.22	225.53 ± 95.28	0.546
WBC	8.61 ± 4.62	8.53 ± 4.95	8.66 ± 4.47	0.909
Limph	18.48 ± 8.39	15.79 ± 6.86	20.18 ± 8.90	0.043
Gluc	6.04 ± 2.34	5.93 ± 2.67	6.12 ± 2.13	0.744
Proteine	64.18 ± 12.62	65.25 ± 7.59	63.47 ± 15.16	0.597
Creat	0.09 ± 0.11	0.13 ± 0.18	0.08 ± 0.02	0.072
Bilirub	13.38 ± 4.76	14.97 ± 6.73	12.33 ± 2.40	0.042
ALT	42.15 ± 30.23	49.24 ± 42.56	36.96 ± 15.15	0.15
ACT	36.63 ± 13.95	39.61 ± 15.85	34.45 ± 12.20	0.19
PI	101.16 ± 15.60	100.21± 10.85	101.83 ± 18.35	0.688
PT	16.99 ± 16.84	20.45 ± 26.08	14.57 ± 1.42	0.546
MHO	0.98 ± 0.12	1.02 ± 0.14	0.96 ± 0.11	0.103
ATPP	42.76 ± 17.47	45.86 ± 16.11	40.60 ±18.28	0.243
Fibr	5.98 ± 2.46	6.59 ± 2.67	5.56 ± 2.26	0.103

Table II. Descriptive statistics of MoCA subscales and total score

	Average	SD	Min	25%	50%	75%	Max
Visuospatial/ executive functioning	2.23	1.09	0.00	2.00	2.00	3.00	5.00
Naming	2.98	0.20	1.00	3.00	3.00	3.00	3.00
Attention	4.75	1.20	1.00	4.00	5.00	6.00	6.00
Language	1.61	0.91	0.00	1.00	2.00	2.00	3.00
Abstract thinking	1.18	0.67	0.00	1.00	1.00	2.00	2.00
Delayed Recall	1.63	1.45	0.00	0.00	2.00	3.00	5.00
Orientation	5.81	0.46	4.00	6.00	6.00	6.00	6.00
MoCA total score	20.16	3.46	13.00	18.00	21.00	22.00	28.00

did not reach statistical significance [15]. Another study, in France, revealed in more than 1/3 of patients, signs of cognitive impairment on discharge from the intensive care unit, especially in the form of dysexecutive syndrome, characterized by inattention, disorientation and decreased executive functioning [16]. In a study by Alemanno et al. (2021), 80% of patients with severe COVID-19 had memory deficits, visuospatial/executive functioning, abstraction, orientation and naming one month after discharge [17]. It is known that the hippocampus, a part of the brain involved in memory processes, is particularly vulnerable to damage associated with COVID-19 [18]. This may explain in some way the presence of persistent memory impairment in those who recovered from COVID-19.

Studies have also shown that patients admitted to the intensive care unit with respiratory distress syndrome and received invasive treatments such as pulmonary ventilation and sedation are at higher risk of cognitive impairment [19, 20]. In a meta-analysis of 72 studies conducted by Rogers et al. (2020), neurological and mental disorders were observed both in the acute period of coronavirus infections and after that (age of hospitalized patients ranged from 12 to 68 years) [21]. Three months after discharge from the intensive care unit, 40% of patients had general cognition scores corresponding to moderate traumatic brain injury, and 26% had indicators such as those with mild Alzheimer's disease, and in many patients the disorder persisted for 12 months [22].

Some researchers predict that a number of COVID-19 survivors will experience long-term cognitive dysfunction and asthenia, creating a «secondary pandemic of neurological disease» that inevitably affects quality of

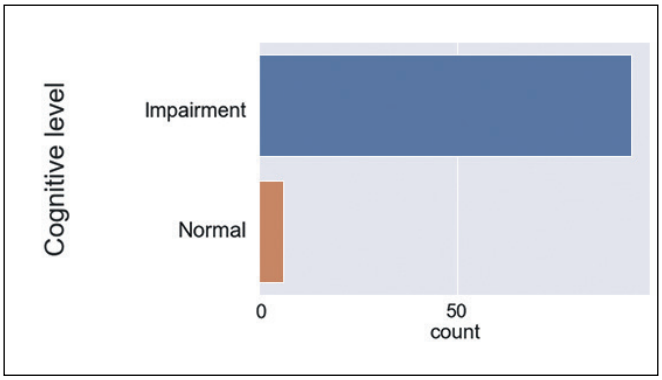

Fig. 1. Cognitive impairment prevalence

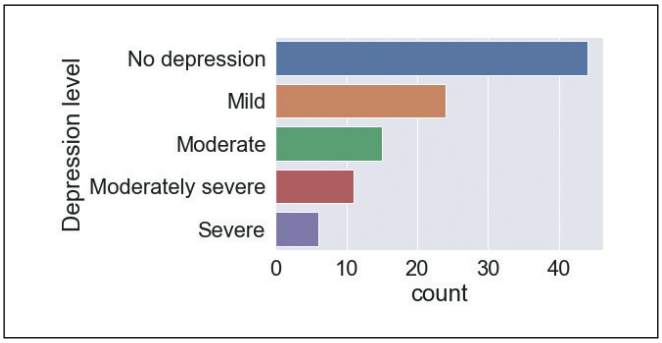

Fig. 2. Depression severity levels

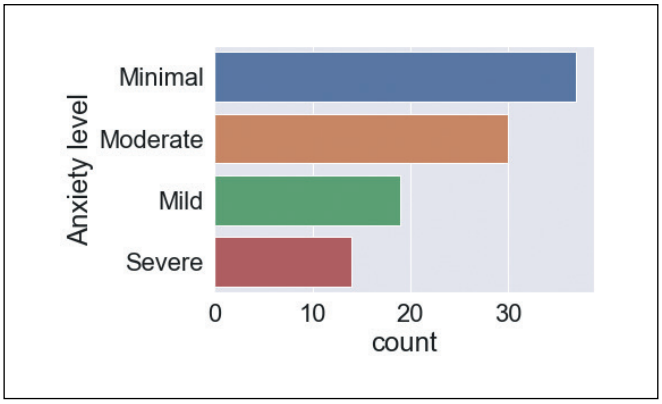

Fig. 3. Anxiety severity levels

life [23,24]. Cognitive dysfunction is one of the most common symptoms reported in Long COVID studies, which occur in approximately 70% of patients [25]. In one study, 86% of participants said that cognitive dysfunction accompanied by memory impairment affected their ability to work. [26].

As we can see, the problem with many studies is that patients are admitted to the hospital in a serious condition and usually mostly elderly. Thus, it is important to determine whether cognitive deficits are specific to COVID-19, or a more general response to oxygen deprivation, acute respiratory distress, and exacerbate pre-existing age-related cognitive decline. It is known, for example, that the survival of serious diseases and age can affect the deterioration of cognitive function.

THE AIM

To study the structure of cognitive impairment in patients who were hospitalized with moderate to severe COVID-19 pneumonia. Investigate the presence of correlation with demographic, clinical parameters, as well as the emotional state of the patient.

MATERIALS AND METHODS

As part of psychiatric screening, PHQ-9 depression and GAD-7 anxiety questionnaires were used to study psychopathological symptoms. Cognitive functions were assessed using the MOCA test. Demographic, clinical, pharmacological and laboratory data were extracted from medical records. Study design - cross-sectional.

Statistical analysis: Data presented as mean ± standard deviation. Cronbach's alpha was used to assess consistency and reliability of psychometric tools. For correlation analysis Spearman correlation coefficient was used. Two-sided test for two samples was used to compare the group means. Data analysis was performed in EzR v.1.54. Data visualization was dome by using Python programming language with seaborn, matplotlib packages. As a statistically significant was considered p level lower than 0.05.

RESULTS

DEMOGRAPHICAL CHARACTERISTICS

A total of 100 inpatients with moderate to severe viral COVID-19 pneumonia were enrolled into the study after signing the informed consent. 52 were females and 48 males. Mean age was 59.01 ± 11.21. 53 patients were working by the moment of enrollment and 47 were retired. 51 patients finished only high school and 49 obtained university education.

There was no difference in mean age depending on gender ($p = 0.784$), and educational level ($p = 0.283$), but those, who were working, were younger (53.08 ± 8.70 against 64.26 ± 10.60 in non-working, $p = 0.000$.

96 patients (93%) from the study group denied the presence of any organic or other mental disorders. 1 patients (2%) reported a previously diagnosed comorbid Depressive Disorder, 1 patient (2%) reported a comorbid Bipolar Disorder, and 2 patients (3%) reported Anxiety Disorder.

CLINICAL CHARACTERISTICS

Clinical characteristics of study sample are presented in Table I. There was a significant difference between males and females in Hb, HCT, Limph, Bilirub levels.

COGNITIVE FUNCTIONING

The mean MoCA score was 20.16 ± 3.46, indicating cognitive impairment (Table II).

94 patients had cognitive impairment (MoCA score < 26) and only 6 had normal cognitive functioning (Fig.1).

There was no significant difference in patients with different gender ($p = 0.894$), and education level ($p = 0.324$), while cog-

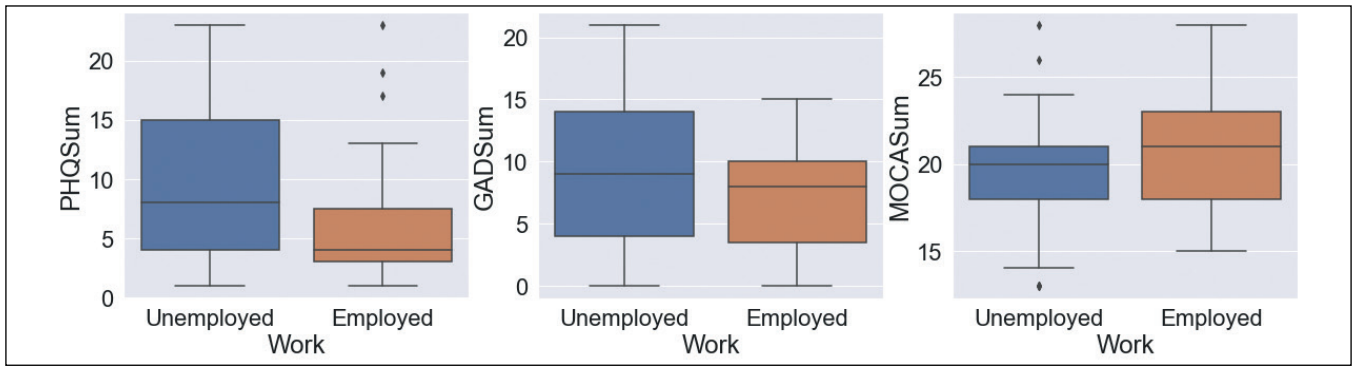

Fig. 4. Boxplot of difference between working and unemployed/retired participants

Table III. Descriptive statistics of PHQ questions and total score

	Average	SD	Min	25%	50%	75%	Max
PHQ 1	1.09	1.16	0.00	0.00	1.00	2.00	3.00
PHQ 2	0.81	0.84	0.00	0.00	1.00	1.00	3.00
PHQ 3	1.51	1.11	0.00	1.00	1.00	3.00	3.00
PHQ 4	1.43	1.12	0.00	1.00	1.00	3.00	3.00
PHQ 5	1.10	1.02	0.00	0.00	1.00	2.00	3.00
PHQ 6	0.52	0.78	0.00	0.00	0.00	1.00	3.00
PHQ 7	0.50	0.89	0.00	0.00	0.00	1.00	3.00
PHQ 8	0.82	0.98	0.00	0.00	0.00	2.00	3.00
PHQ 9	0.20	0.44	0.00	0.00	0.00	0.00	2.00
PHQ Total score	7.98	6.16	1.00	3.00	6.00	13.00	23.00

Table IV. Descriptive statistics of GAD questions and total score

	Average	SD	Min	25%	50%	75%	Max
GAD 1	1.21	1.04	0.00	0.00	1.00	2.00	3.00
GAD 2	1.19	0.98	0.00	0.00	1.00	2.00	3.00
GAD 3	1.34	0.98	0.00	1.00	1.00	2.00	3.00
GAD 4	1.35	0.92	0.00	1.00	1.00	2.00	3.00
GAD 5	1.06	1.05	0.00	0.00	1.00	2.00	3.00
GAD 6	1.25	1.04	0.00	0.00	1.00	2.00	3.00
GAD7	0.92	0.93	0.00	0.00	1.00	1.00	3.00
GAD Total score	8.32	5.52	0.00	4.00	9.00	12.00	21.00

nitive performance was better in patients who was working by the moment of study.

However, this may also be explained by age difference and negative correlation between age and cognitive performance ($r = -0.574$, $p = 0.000$). Hospitalization status had no effect on cognitive performance ($p = 0.889$), as well as comorbid cardiac pathology ($p = 0.971$).

The most severe impairment was seen in visuospatial and executive functioning, abstract thinking, attention and delayed recall, while other cognitive domains found to be relatively intact.

DEPRESSION LEVEL

The mean total score for PHQ-9 was 7.98 ± 6.16, indicating mild depression (Table III). Cronbach's alpha for PHQ-9 was 0.88, indicating excellent consistency and reliability of PHQ-9 for measuring depression in Ukrainian population.

Most patients (44) had no signs of depression, 24 patients had mild symptoms of depression, 15 had moderate depression, 11 had moderately severe depression and 6 had severe depression (Fig.2).

There was no significant difference depending on gender ($p = 0.771$) or education level ($p = 0.561$). The total score was different depending on working status: patients, who had a job by the moment of participation, had significantly lower scores, than patients, who were unemployed (5.76 ± 4.70 vs 9.94 ± 6.66 respectively, $p = 0.000$).

Hospitalization status also had no significant impact on PHQ total score ($p = 0.247$), as well as comorbid cardiac pathology ($p = 0.333$).

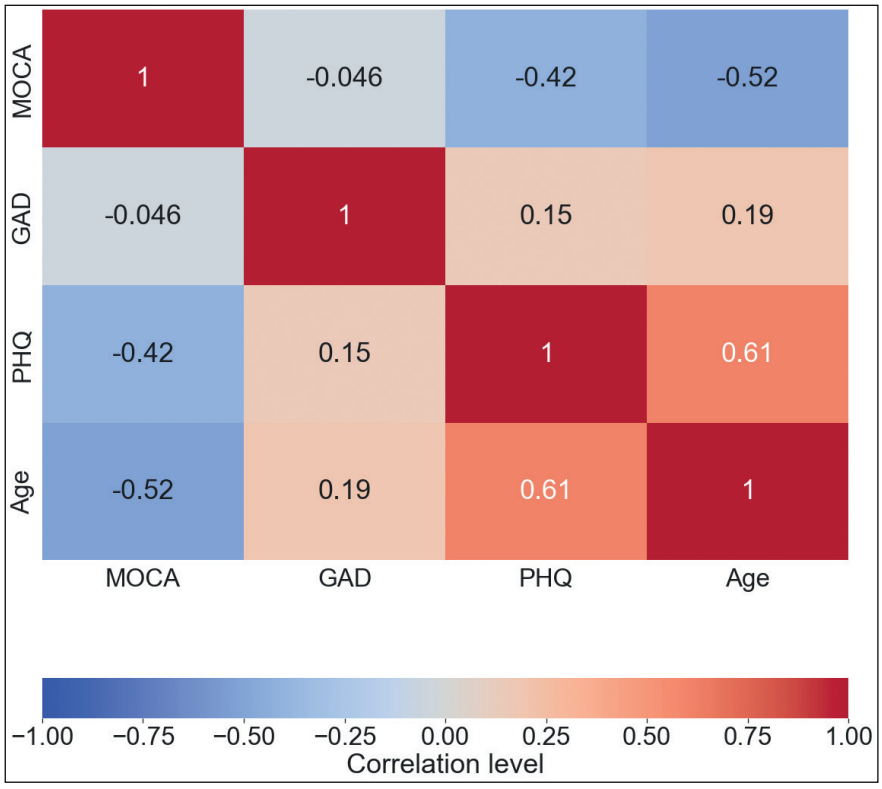

Fig. 5. Correlation between cognitive performance (MoCA score), age, anxiety (GAD score), and depression (PHQ score).

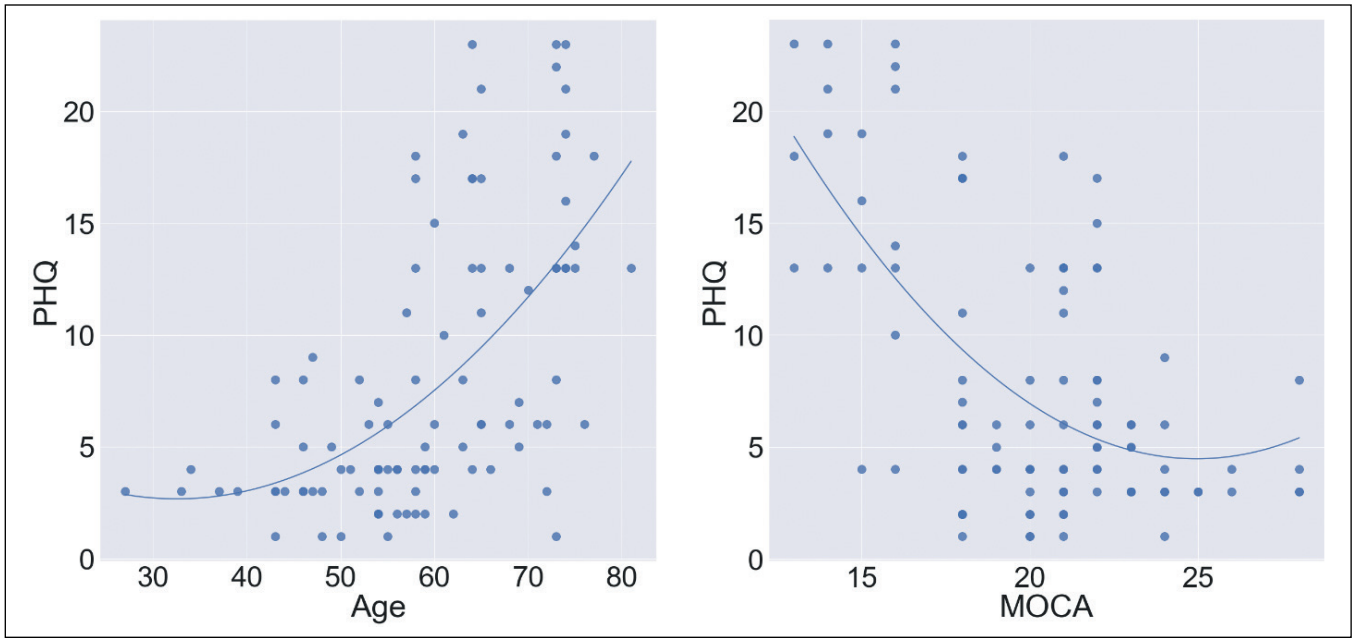

Fig. 6. Scatterplots between PHQ total score, age in years and MoCA total score

ANXIETY LEVELS

The mean total score for GAD-7 was 8.32 ± 5.52, indicating mild anxiety (Table IV). Cronbach's alpha for GAD-7 was 0.90, indicating excellent consistency and reliability of GAD-7 for measuring depression in Ukrainian population.

Most patients (37) had minimal anxiety level, while not much less (30) had moderate level, while 19 patients had mild and 14 – severe anxiety level (Fig. 3).

There was no significant difference depending on gender ($p = 0.702$). Patients with university education had significantly higher level of anxiety comparing to patients only with high school education (9.51 ± 5.58 and 7.17 ± 5.26 respectively, $p = 0.033$). The total GAD score was different depending on working status: patients, who had a job by the moment of participation, had significantly lower scores, than patients, who were unemployed (7.02 ± 4.30 vs 9.47 ± 6.22 respectively, $p = 0.026$, (Fig.4).

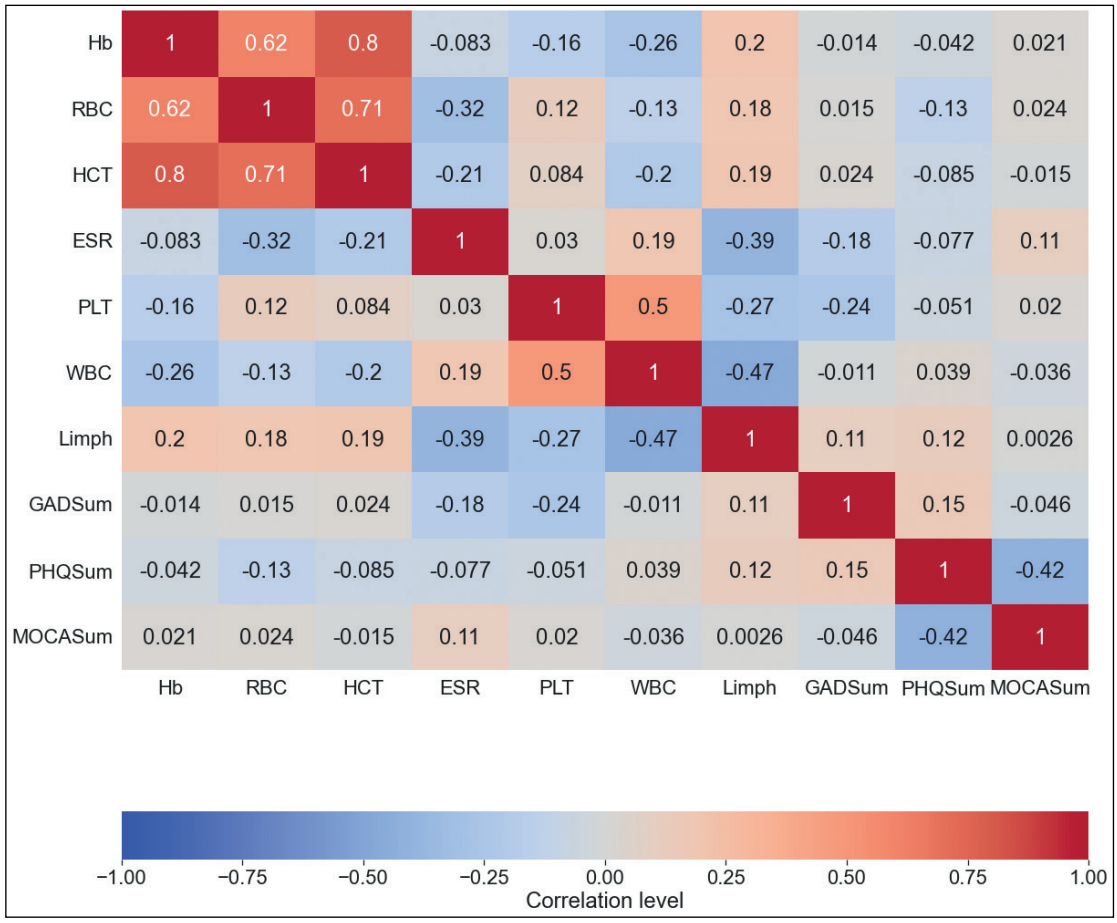

Fig. 7. Correlation between anxiety (GAD score), depression (PHQ score), cognitive performance (MoCA score) and blood element measurements

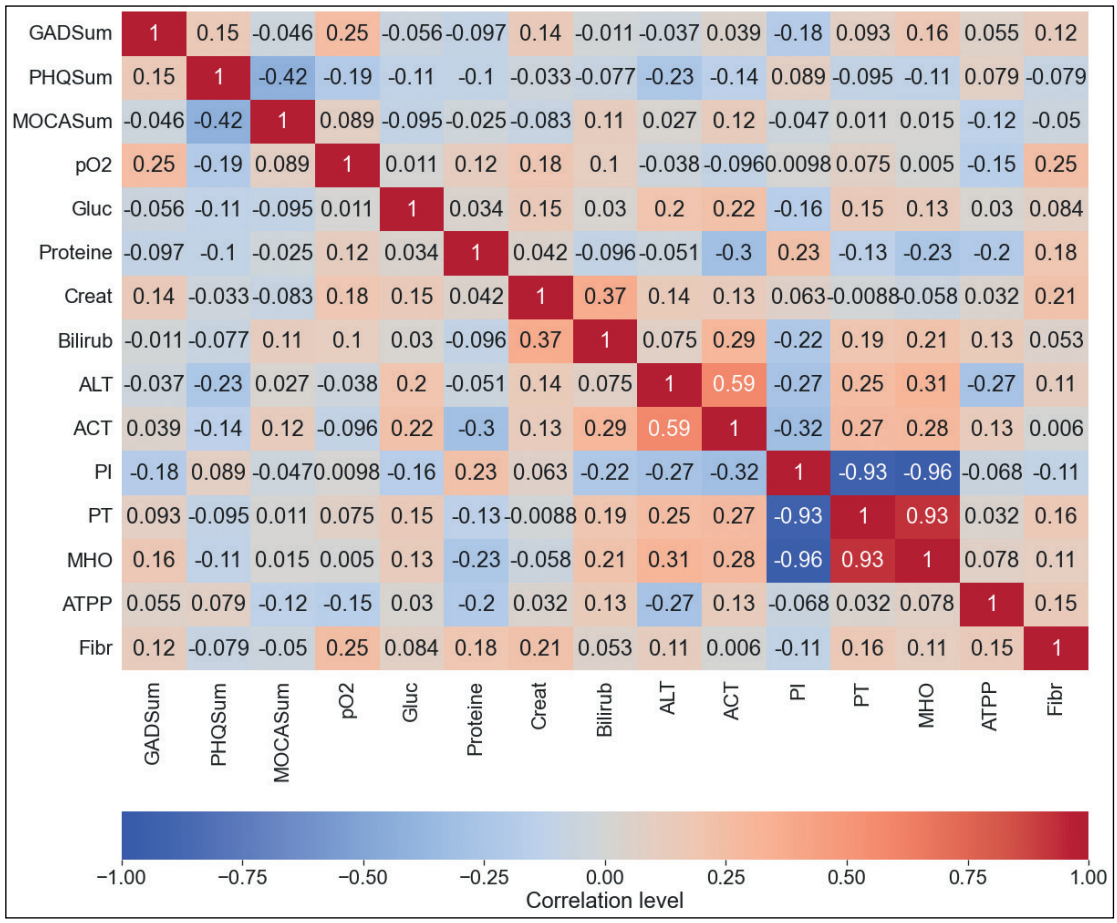

Fig. 8. Correlation between anxiety (GAD score), depression (PHQ score), cognitive performance (MoCA score) and biochemical measures

Hospitalization status had no significant impact on GAD total score (p = 0.122), however, comorbid cardiac pathology had. Anxiety level was lower in patients with the comorbid cardiac pathology with mean score 7.08 ± 5.26, while in patience without comorbid heart diseases it was 9.37 ± 5.56 (p = 0.038)

CORRELATION OF COGNITIVE FUNCTIONING WITH EMOTIONAL STATE AND CLINICAL FEATURES

Intercorrelation of age, anxiety level, depression level and cognitive performance are presented at correlation heatmap matrix (Fig. 5).

There was no statistically significant correlation between age and anxiety level (p = 0.055), but significant moderate positive correlation was found between age and depression (p = 0.000), as well as significant moderate negative correlation was found between age and cognitive performance (p =0.000). No significant correlation was found between anxiety and depression (p = 0.124), and anxiety and cognitive performance (p = 0.65). Negative moderate correlation between depression and cognitive performance was found (p = 0.000).

However, a visual analysis revealed, that while the relationship between cognitive functioning and age was linear, a relationship between PHQ score and age tends to be non-linear, as well as between PHQ and MoCA scores (Fig. 6).

No significant correlation was found between psychological outcomes and blood cells clinical tests (Fig.7)

Significant positive mild correlation was also found between GAD score and pO2 (r = 0.253, p = 0.047). No significant correlation was found between other clinical outcomes and psychometric measures (Fig 8.).

DISCUSSION

Cognitive performance is impaired in 94% of COVID-19 patients. Such huge percent cannot be explained only by age, because studies report that the amount of cognitively impaired elder people vary from 40% to about 60%, but not > 90% [27]. This allows to suggest that COVID-19 has a serious impact on cognition, especially in elder people. Considering that in our study MoCA results related to age, we may suggest that cognitive reserves are an important protective factor against devastating effect of COVID.

Another interesting finding was that among different domains only visuospatial and executive functioning, abstract thinking, attention and delayed recall were severely impaired, while other domains stayed relatively intact.

Patients after COVID-19 also tend to have a mild depressive and anxiety state. Anxiety levels were higher than depressive levels, but not connected to cognitive functioning. Education level seems to be an important factor, that increases anxiety in patients after COVID-19 [28]. The possible explanation may be higher cognitive processing of information in people with university education that leads to higher levels of anxiety. This may be complemented by findings about positive correlation between anxiety and pO2 and negative between anxiety and comorbid cardiac pathology. However, this requires further studies to reveal.

Another interesting finding was non-linear relationship between cognitive performance and depression, that allows to suggest rapidly evolving depressive mood in persons with severe cognitive impairment after COVID-19.

Cognitive and emotional state of patients after COVID-19 was highly connected with working status, however, ability to work relates to age by itself, therefore, the real factor of better emotional and cognitive performance may be younger age. Moreover, this connection seems to be non-linear in case of depression, leading to rapid increase in chances to get a depression after the age of 60.

Despite patients with different gender had some difference in clinical results, this didn't affect psychological state and cognitive performance of patients. Therefore, emotional state after COVID-19 seems to be unrelated to clinical characteristics and may be dependent on cognitive processing and attitude to disease, as well as other psychological and social factors.

CONCLUSIONS

Significant cognitive impairment was presented in almost all patients with COVID-19, that cannot be explained only by age**.** There was a selective impairment in domains of visuospatial and executive functioning, abstract thinking, attention and delayed recall, while other domains stayed relatively intact. The absence of correlation with biochemical outcomes allows to suggest the possible specific impact of COVID-19 on brain function. Symptoms of mild anxiety and depression are also common. Worse emotional state is connected with worse cognitive performance and depressive mood is very common in patients with severe cognitive impairment.

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