CLINICAL FEATURES OF ANXIETY DISORDER IN POST-COVID-19 SYNDROME AND FINDING OF ITS PREDICTORS

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Abstract: the article summarizes and describes clinical features of anxiety disorders in post-COVID-19 syndrome. Mental and neurological disorders occupy a leading place in the structure of post-COVID syndrome. Recent studies indicate an increase in the incidence of anxiety disorders in individuals with COVID-19. However, no clinical or laboratory features of the post-COVID anxiety disorders have been identified. Therefore, our study aimed to describe the clinical features of anxiety disorders in the post-COVID period and to develop a mathematical prognostic model to identify potential predictors of post-COVID anxiety disorder. We conducted a case-control clinical study, which included 145 males and females, which were divided into 2 groups, namely: group 1 - patients who became ill with COVID-19 during the last 6 months and group 2 - persons who were not ill with COVID-19 during the last 6 months. The clinical interview included the registration of symptoms of the debut and the time of the debut relative to the episode of COVID-19. The Beck anxiety inventory was used for the assessment of the overall level of anxiety. The State-trait anxiety inventory was used to assess state and trait anxiety. Statistical analysis of the data was performed using the program EZR Statistics 1.54. Anxiety disorders during the first 6 months after COVID-19 develop more often than those who have not had the disease in the last six months. Patients who had COVID-19 in the last 5-24 weeks have an increased risk of anxiety disorders during this period and therefore require close medical supervision and sufficient awareness of the likely symptoms. People with a post-COVID anxiety disorder reported the presence of autonomic symptoms, including excessive sweating and tachycardia, a feeling of inner emptiness, as well as circadian rhythm disorders in the form of difficulty falling asleep and waking up at the desired time. It should be noted that the overall frequency of detection of anxiety disorders in the post-COVID period is increasing. It has been established that the risk of developing post-COVID disorder decreases with knowledge of the fact of contact with an infected person before the COVID onset and increases with a heightened level of prior personal anxiety. Circadian rhythm disorders, in particular sleep phase shift and abnormal fatigue, may be predictors of post-COVID anxiety disorder.

Key words: mood disorders, anxiety, circadian rhythm, circadian clocks, post-acute COVID-19 syndrome, fatigue, sleep wake disorders

Introduction. The COVID-19 pandemic continues to affect people around the world and damage the health and political systems of the states. Since most patients survive this disease, the problem of the long-term consequences of this infection is a pressing issue (Jiang & McCoy, 2020). A year ago, the existence of post-COVID syndrome was questioned, but it was assumed that its existence may be due to the persistence of symptoms for 6 months after the disease (Lamprecht, 2020). It is generally accepted that postcovid syndrome includes symptoms that appear after the 4th week after the disease persisting for a later period and are directly related to the coronavirus infection (Carod Artal, 2021). However, now more and more researchers are discussing the symptoms of the whole syndrome and trying to classify it based on various approaches. For example, it is proposed to divide the symptoms that occur after COVID-19 according to the time of their occurrence (Fernández-de-las-Peñas et al., 2021), namely:
- Symptoms potentially associated with acute COVID-19 – up to 4–5 weeks;
- Acute post-COVID – from week 5 to week 12;
- Long post-COVID – from week 12 to week 24;
- Persistent post-COVID – more than 24 weeks.

Mental and neurological disorders occupy a leading place in the structure of post-COVID syndrome. Many authors point to the persistence of pathological fatigue, anxiety disorders, depression, sleep disorders, and circadian rhythm disorders, as well as disorders of the autonomic nervous system in the post-COVID period (Dani et al., 2021; El Sayed et al., 2021; Szekanecz & Vályi-Nagy, 2021; Zolotovskaya et al., 2021). These disorders persist in patients even 6 months after the disease. Therefore, many researchers have studied
not only the specifics of drug treatment but also non-pharmacological methods of COVID-19 treatment and its effects during a pandemic, including exposure to physical factors, physical rehabilitation, and psychotherapy (Hussain et al., 2021; Jimeno-Almazán et al., 2021; PLAKUN, 2020).

Recent studies indicate an increase in the incidence of anxiety disorders in individuals with COVID-19 (Yong, 2021). Studies show an increase in the prevalence of anxiety disorders with the spread of any socially significant disease that causes an epidemic or pandemic, as it is an important traumatic factor (de Sousa Moreira et al., 2021). However, what makes SARS-CoV2 even more interesting and draws scientific attention is that it is neurotropic. Neuroinvasion of SARS-CoV-2 can be realized by blood transfer to tissues with a high level of vascularization, by trans-synaptic transfer from infected neurons, through the olfactory nerve, or the blood-encephalic barrier (Lukiw et al., 2020). This causes complex multivariate manifestations of the post-COVID syndrome.

The neuropsychiatric manifestations of post-COVID syndrome are partly explained by an imbalance of neurotransmitters such as serotonin, dopamine, and the hormone melatonin, which may occur against the background of a cytokine storm due to severe infectious disease (Attademo & Bernardini, 2021). Decreases in serotonin levels with increasing severity of COVID-19 have been reported and may be used as a biomarker of disease progression (Soria-Castro et al., 2021). The determination of bioactive substances’ blood levels can be useful for the improvement of a diagnostic process of post-COVID anxiety disorder due to the key role in the pathogenesis of affective disorders. However, to date, no clinical or laboratory features of the course of anxiety disorders in the post-COVID syndrome have been identified. Therefore, our study aimed to describe the clinical features of anxiety disorders in the post-COVID period and to develop a mathematical prognostic model to identify potential predictors of post-COVID anxiety disorder.

**Methods.** We conducted a case-control study, which included 145 males and females, aged 18 to 59 years, who consulted a family physician for a preventive examination. All respondents were divided into 2 groups according to the anamnesis data, namely: group 1 (experimental) - patients who became ill with COVID-19 during the last 6 months (n = 69) and group 2 (control) - persons who were not ill with COVID-19 during the last 6 months (n = 76). Criteria for inclusion in group 1: COVID-19 in the anamnesis, confirmed by PCR testing, post-COVID syndrome (5-24 weeks from the onset of symptoms of COVID-19), age from 18 to 59 years. The criteria for inclusion in the control group was the absence of COVID-19 in the anamnesis. The criteria for exclusion were the presence of concomitant severe somatic pathology, a history of mental disorders before COVID-19, including anxiety disorder at the time of the onset of coronavirus infection, the appearance of symptoms of coronavirus infection 5 weeks ago and later. Patients with COVID-19 were surveyed on the severity of the clinical course and awareness of the previous contact with an infected person.

The clinical interview included the registration of symptoms of the debut and the time of the debut relative to the episode of COVID-19.

To assess the overall level of anxiety, the Beck anxiety inventory was used, according to which the sum of scores less than 22 indicates low anxiety, 22-35 – moderate, and 36-63 – potentially concerning levels of anxiety.

The State-trait anxiety inventory was used to assess state and trait anxiety. Each scale contains 20 questions, which should be answered with the help of Likert 4-point frequency scale, ranging from 1 point (never) to 4 points (very often). Personal anxiety means a motive and an acquired behavioral attitude that forces a person to perceive objectively safe things as a source of danger, that is, to react with anxiety that does not correspond to the real conditions. Situational anxiety characterizes a person’s condition at the time of examination, which occurs as an emotional response to an extreme or stressful situation, can vary in intensity, and change dynamically. The sum of points on each scale varies from 20 to 80, along with the larger values corresponding to a more pronounced anxiety syndrome. It is considered that <30 points is a low level of anxiety, 31-45 points – average, >45 points – high.

All patients were provided with comprehensive information on the possible benefits and outcomes of the study. Study participants gave informed consent to participate in the study before the start of all procedures. The study was approved by the Bioethics Committee of Poltava State Medical University and conducted by the principles of Good Clinical Practice (ICH E2 (R6) GCP).

Statistical analysis of the data was performed using the program EZR Statistics 1.54 (from 20.12.2020), which is publicly available on the website of the Medical University of Jichi, Japan.

The normality of the distribution of the obtained results was checked using the Shapiro-Wilk test. Normally distributed quantitative indicators are presented as the mean value (M) and the standard error of the mean (m). Qualitative indicators are presented in the form of absolute quantity (n) and percent (%). Analysis of differences between the two groups was performed using the T-test for independent groups. Multiple comparisons of qualitative indicators were performed using the criterion χ² with Yates correction. To determine the relationship between qualitative variables, a risk ratio with a 95% confidence interval was calculated. To
determine the predictors of the development of post-COVID anxiety disorder, a multivariate binary logistic regression analysis was performed by the Wald reverse inclusion method with a threshold for inclusion \( p < 0.05 \) and for exclusion \( p = 0.1 \). Quality assessment of the prognostic model was performed by ROC analysis with the choice of maximum sensitivity and specificity. For all measurements, the critical value was \( p < 0.05 \), at which the results were considered statistically significant.

**Results.** The mean age of patients in group 1 was 37.6±7.3 years and in group 2 – 39.4±6.9 years. Group 1 included 22 (32%) men and 47 (78%) women, and group 2 – 31 (41%) men and 33 (66%) women. No statistically significant age (\( p = 0.436 \)) and gender (\( p = 0.311 \)) differences were found.

25 patients (36%) from group 1 reported a mild course of the disease, 28 (41%) - moderate and 16 (23%) - severe. Among them, only 26 (38%) patients knew about contact with an infected person before the onset of COVID, which can be an additional psychotraumatic factor.

In group 1, anxiety disorders were found in 46 (67%) patients, and group 2 – in 37 (49%) people. Among those who underwent COVID-19, the appearance of anxiety symptoms in the period from 5 to 12 weeks was noted by 29 (63%) people, and from 12 to 24 weeks – 17 (37%) people. It was found that in group 1 the frequency of anxiety is higher (\( \chi^2 = 4.54, p = 0.34 \)) compared to group 2. For people with COVID-19 the risk of developing anxiety disorders is 1.24 times higher (\( RR = 1.243, 95\% CI 1.06-1.49, p=0.036 \)).

Complaints of pathological fatigue (in 41 people - 89%), constant feeling of danger (in 39 people - 85%), difficulties in falling asleep (in 35 people - 76%) and waking up (in 33 people - 72%), excessive sweating (in 29 people - 63%), tachycardia (in 27 people - 59%) and feelings of inner emptiness (in 25 people - 54%) prevailed among patients of group 1. Along with this, in group 2 the most common complaints were a constant feeling of danger (in 23 people - 62%) and pathological fatigue (in 21 people - 57%). This data is summed up in table 1.

It was determined that in group 1, difficulties in falling asleep and waking up, tachycardia, excessive sweating, a constant sense of danger, and pathological fatigue were more common in group 1 than in group 2. Along with this, it should be noted that a constant sense of danger and pathological fatigue are noted by the majority of patients in both groups.

In group 1, the average score on the Beck anxiety inventory was 39.6 ± 1.7 points, and in group 2 - 23.3 ± 2.1 points, which was statistically significantly higher in group 1 (\( p = 0.007 \)).

Among group 1 patients, 11 (24%) had low anxiety, 17 (37%) had moderate anxiety, and 18 (39%) had severe anxiety, while in group 2 20 patients (54%) had low anxiety, 8 (22%) – moderate and 9 (24%) – severe, concerning anxiety, as shown in Fig.1.

There was a statistically significantly higher frequency of moderate and severe anxiety in group 1, compared with group 2, where a low level prevails (\( \chi^2 = 7.91, p = 0.019 \)). Thus, patients who had COVID-19 in the last 6 months show a higher level of anxiety, which may be a component of the post-COVID syndrome.

The average score of trait anxiety in group 1 was 47.2±3.9, and in group 2 – 32.8±3.4 points, which had no statistically significant differences (\( p=0.134 \)). In addition, the level of state anxiety in group 1 was statistically significantly higher (\( p=0.003 \)) compared with group 2 and was 36.1±2.5 and 32.7±3.1, respectively.

Low levels of state anxiety were found in 10 (22%) patients in group 1 and 17 (46%) in group 2, moderate in 15 (33%) of persons in group 1 and in 11 (30%) of group

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n=46)</td>
</tr>
<tr>
<td>Fear of death</td>
<td>18 (39%)</td>
</tr>
<tr>
<td>Difficulties in falling asleep</td>
<td>35 (76%)</td>
</tr>
<tr>
<td>Difficulties in waking up</td>
<td>33 (72%)</td>
</tr>
<tr>
<td>Constant sense of danger</td>
<td>39 (85%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Impaired concentration</td>
<td>13 (28%)</td>
</tr>
<tr>
<td>Feelings of inner emptiness</td>
<td>25 (54%)</td>
</tr>
<tr>
<td>Pathological fatigue</td>
<td>41 (89%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Tachycardy</td>
<td>27 (59%)</td>
</tr>
<tr>
<td>Excessive sweating</td>
<td>29 (63%)</td>
</tr>
<tr>
<td>Agitation</td>
<td>15 (33%)</td>
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</tbody>
</table>

Table 1. The structure of neuropsychiatric complaints of patients with anxiety disorders in the post-COVID period in comparison with respondents who had anxiety disorders but did not suffer from COVID-19, abs. (%)
2, and severe in 21 (46%) and 9 (24%), respectively. The level of trait anxiety was low in 13 (28%) people in group 1 and 16 (43%) in group 2, moderate – in 21 (46%) in group 1 and 13 (35%) in group 2 and severe – in 12 (26%) and 8 (22%) accordingly, which is presented in fig.2. It was found that the level of state anxiety in individuals with COVID-19 was statistically significantly higher ($\chi^2 = 6.33, p = 0.043$) over the level of individuals with anxiety disorders but not suffering from coronavirus infection. However, the level of trait anxiety did not have significant differences between groups ($\chi^2 = 2.04, p = 0.361$).

To identify predictors of post-COVID anxiety disorder, a regression analysis of data from 69 patients in group 1 who had COVID-19 was performed. The analysis included complaints, features of the clinical course, severity of anxiety and its components, as well as anamnestic data. The model is summarized in 12 steps, with the remaining 5 independent predictors, which are presented in table.2.

We found that knowledge of the fact of contact with an infected person before the COVID-19 episode, difficulty falling asleep, difficulty waking up at the desired time, pathological fatigue, and level of personal anxiety all are of prognostic value for the risk of developing a post-COVID anxiety disorder. To be exact, the chance of developing anxiety in the post-COVID period decreases 2.4 times (OR=0.42, 95% CI 0.21-0.83, p=0.036) when knowing the fact of contact with the infected before the disease and increases by 2.9 times (OR=2.9, 95% CI 1.7-4.2, p=0.008) in the presence of complaints about the difficulty of falling asleep, 1.4 times (OR=1.4, 95% CI 1.07-2.8, p=0.042) with difficulties in waking up, 2.1 times (OR=2.1, 95% CI 1.6-3.7, p=0.016) in the presence of complaints of pathological fatigue, as well as 1.09 times (OR=1.09, 95% CI 1.02-1.19, p=0.027) for each point of personal anxiety.

Using the multivariate binary logistic regression analysis, we built a prognostic model of the risk of post-COVID anxiety disorder, which is described by equation 1:

![Figure 1. Level of anxiety in patients who had COVID-19 in the last 6 months, compared with respondents who had anxiety disorders but did not have COVID-19.](image1)

![Figure 2. Level of trait and state anxiety in patients who had COVID-19 in the last 6 months, compared with respondents who had anxiety disorders but did not have COVID-19.](image2)

Table 2. The structure of complaints of patients with anxiety disorders in the post-COVID period in comparison with healthy respondents

<table>
<thead>
<tr>
<th>Parameter</th>
<th>В±m coefficient</th>
<th>Відношення шансів</th>
<th>95%-% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Const</td>
<td>-7,01±3,66</td>
<td>-</td>
<td>-</td>
<td>0,035</td>
</tr>
<tr>
<td>X1</td>
<td>-0,34±0,11</td>
<td>0,42</td>
<td>0,21-0,83</td>
<td>0,036</td>
</tr>
<tr>
<td>X2</td>
<td>1,09±0,18</td>
<td>2,9</td>
<td>1,7-4,2</td>
<td>0,008</td>
</tr>
<tr>
<td>X3</td>
<td>3,5±1,7</td>
<td>1,4</td>
<td>1,07-2,8</td>
<td>0,042</td>
</tr>
<tr>
<td>X4</td>
<td>3,2±1,1</td>
<td>2,1</td>
<td>1,6-3,7</td>
<td>0,016</td>
</tr>
<tr>
<td>X5</td>
<td>2,3±0,78</td>
<td>1,09</td>
<td>1,02-1,19</td>
<td>0,027</td>
</tr>
</tbody>
</table>

Note. X1 – the fact of contact with an infected person before the COVID-19, X2 – difficulty falling asleep, X3 – difficulty waking up, X4 – pathological fatigue, X5 – level of personal anxiety.
The optimal test limit was selected by the Youden’s Index calculation method. The optimal decision limit was Pgr. = 0.393: for P (patient) ≥ Pgr. – you can predict the risk of post-COVID anxiety disorder, for P (patient)<Pgr. – it is possible to predict the absence of development of post-COVID anxiety disorder.

To analyze the adequacy of the constructed model, we analyzed the curve of operational characteristics, which corresponds to our regression equation and is presented in Fig.3.

The accuracy of the constructed prognostic model was evaluated according to the training sample and was 94.2% (95% CI 84.3-99.8%). Point and interval estimates of the efficiency of the regression model were calculated from the matrix of classifications and were: - t

- the probability of a correctly predicted positive result (sensitivity) when using this model – 88.9% (95% CI 83.8-94.0%);
- probability of correctly predicted negative result (specificity) - 89.5% (95% CI 82.8-96.2%);
- predictability of a positive test result – 89.1% (95% CI 84.9-93.3%);
- predictability of a negative test result – 91.3% (95% CI 89.9-92.7%).

The constructed five-factor model revealed the dependence of the risk of post-COVID anxiety disorder on factor traits, the area under the ROC curve AUC = 0.94 ± 0.03 (95% CI 0.84 - 0.99) statistically significant (p <0.001) exceeds 0.5, which is evidence of the adequacy of the constructed model.

**Discussion.** Anxiety disorders during the first 6 months after COVID-19 develop more often than those who have not had the disease in the last six months. In our study, anxiety disorders were found in 67% of convalescents, while current studies show a frequency of persistence of post-COVID anxiety disorder 1 month after the disease in 42% of patients and 6 months after the onset of symptoms in 23% (Huang et al., 2021; Sher, 2021).

The development of anxiety disorders in the post-COVID syndrome occurs mainly during the period between 5-12 weeks after COVID, which corresponds to the period of acute post-COVID according to the classification proposed (Fernández-de-las-Peñas et al., 2021).

Thus, patients who had COVID-19 in the last 5-24 weeks have an increased risk of anxiety disorders during this period and therefore require close medical supervision and sufficient awareness of the likely symptoms. The level of anxiety was also higher in those who had COVID-19, as evidenced by a cross-sectional study of the German population (Bäuerle et al., 2020). Elderly vulnerability to the development of anxiety symptoms after coronavirus infection has also been reported (Bergman et al., 2020). The increased level of state anxiety found in people with COVID-19 indicates its significant psycho-traumatic potential, combined with neurotropic effects, which may increase the risk of mental disorders in the post-COVID period.

Anxiety disorders after COVID-19, as well as in its absence in the amnestic, are characterized by complaints of increased fatigue and a constant feeling of danger. However, in addition, people with a post-COVID anxiety disorder reported the presence of autonomic symptoms, including excessive sweating and tachycardia, a feeling of inner emptiness, as well as circadian rhythm disorders in the form of difficulty falling asleep and waking up at the desired time. It is thought that certain symptoms of post-COVID syndrome may be associated with immune-mediated damage to the autonomic nervous system, causing dysfunction of the autonomic nervous system (Dani et al., 2021; Larsen et al., 2021).

The COVID-19 pandemic caused serious sleep and sleep patterns disorders in all individuals. We found a delay in falling asleep and waking up, which may indicate a delayed sleep phase disorder. Recent studies emphasize a shift in circadian rhythm toward later falling asleep and an increase in daytime sleep in all occupational groups and a decrease in sleep quality and duration due to affective symptoms. (Epstein et al., 2021; Gupta et al., 2020). It is recommended to use drugs according to chronobiological strategy in the treatment of coronavirus infection since the role of a key component of the regulation of human circadian rhythm – the BMAL1 gene – has been established in the replication of SARS-CoV-2 (Zhuang et al., 2021). Sleep control in the human body depends on the balance between sleep-wake cycles and circadian rhythms realized by peripheral oscillators and suprachiasmatic nuclei of the hypothalamus (Kaidashev, 2020). At the same time, slow and fast sleep play different roles in the consolidation of memory depending on its modality, as well as differently affect the psycho-emotional state and
the tendency to develop anxiety (Shkodina et al., 2020). Serotonin and dopamine (Tarianyk et al., 2021) play an important role at different levels of the circadian system. They also play a key role in the pathogenesis of anxiety disorders and can act as a common pathogenetic link to this syndrome.

It is believed that the pathogenesis of the post-COVID syndrome is partly due to increased levels of IL-6 and the involvement of mast cells. Thus, the inflammatory lesion caused by this infection can cause mental disorders in predisposed individuals, in particular those with affective disorders (Anaya et al., 2021). The prognostic model built by us also indicates the level of personal anxiety as a predictor of post-COVID anxiety development. Knowledge of contact with a coronavirus-infected person before a diagnosis of COVID-19 reduced the risk of post-COVID anxiety disorder in the surveyed respondents. In addition, we found an increased risk of developing an anxiety disorder in the post-COVID period in the presence of complaints of pathological fatigue and circadian rhythm disorders, manifested by difficulty falling asleep and waking up at the desired time.

Further clinical studies are required to determine the relationship between circadian rhythm disorders and anxiety in the post-COVID period in order to optimize the treatment of the post-COVID syndrome. Our study had some limitations, including small sample size and a lack of laboratory and instrumental monitoring of patients with post-COVID symptoms, which should be considered when planning future studies.

**Conclusion.** Summing up, it should be noted that the overall frequency of detection of anxiety disorders in the post-COVID period is increasing. Thus, post-COVID anxiety disorder is of particular importance for the treatment of the long-term effects of acute coronavirus infection. It has been established that the risk of developing post-COVID disorder decreases with knowledge of the fact of contact with an infected person prior to the COVID onset and increases with a heightened level of prior personal anxiety. Circadian rhythm disorders, in particular sleep phase shift and abnormal fatigue, may be predictors of post-COVID anxiety disorder.

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**Authors contribution:** concept, methodology, formal analysis, research, resources, data curation, written - original project preparation, review and editing, visualization, supervision, project administration, acquisition of financing - D.B.

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**REFERENCES:**


Ключові слова: розлади настрою, тривога, циркадний ритм, циркадний годинник, постковидний синдром, втома, розлади циклу сну-неспання