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Emotional and sleep disturbances among patients previously hospitalized due to COVID-19

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Summary

Aim. To evaluate incidence of emotional and sleep disturbances (ESDs) in patients after hospitalization due to COVID-19, identify long-term predictors, and understand their influence on brain fog and quality of life at work (QWL).

Material and methods. Patients of 18 or more years retrospectively reported ESDs (sadness, anxiety, restlessness, insomnia, excessive daytime sleepiness, nightmares), brain fog symptoms (BFS), QWL before COVID-19 and within 0–4, 4–12, and >12 weeks postinfection using paper or online validated questionnaire. Data regarding age, sex, comorbidities, pre-admission therapy, and laboratory results were collected. Finally, the study included 181 hospitalized individuals (mean age 56.02 ± 13.02 years; 37.02% women).

Results. COVID-19 increased 1.6-fold to 2.2-fold incidence of ESDs within 0–4, 4–12, and >12 weeks post-infection (66.85%, 60.77%, and 50.28%, respectively). In the multivariable model, new-onset ESDs after COVID-19 were predicted by hemoglobin levels in the acute phase of infection (OR = 0.64; 95% CI: 0.50–0.80 per g/L; $p = 0.001$). In patients with pre-existing and new-onset ESDs, COVID-19 showed a 1.9-fold and 3.9-fold increase in BFS within >12 weeks post-infection, respectively. Deterioration in QWL >12 weeks post-COVID was associated with age (OR = 0.62; 95% CI: 0.37–0.73 per 10 years; $p < 0.001$), female sex (OR = 3.47; 95% CI: 1.40–8.56; $p = 0.007$), pre-existing (OR = 21.58; 95% CI: 2.57–181.30; $p = 0.005$) and new-onset ESDs (OR = 30.88; 95% CI: 3.85–247.90; $p = 0.001$).

Conclusions. During follow-up, most patients with COVID-19 suffer from ESDs that are predicted by hemoglobin levels. The ESDs increase the risk of concomitant BFS. The ESDs,

particularly sadness, restlessness, insomnia, and excessive daytime sleepiness, strongly affect QWL >12 weeks after COVID-19.

Key words: COVID-19, brain fog, emotional and sleep disturbances

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic resulted in increasing number of post-infectious complications, not only related to the acute phase of disease, but also persisting even within few months since its onset [1, 2]. A recent Polish study showed that more than a half of patients qualified for possible post-traumatic stress disorder (PTSD) diagnosis 3 to 6 months after hospitalization due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [3]. Moreover, the frequency of depressive symptoms was estimated at 11% to 28% within more than 12 weeks following an initial infection [4, 5], whereas sleep difficulties were reported by one in four individuals with long COVID [6].

Current data related to prognostic factors of emotional and sleep disturbances (ESDs) after COVID-19 remains inconclusive. For instance, in a study of 227 Mexican patients assessed 3 months after hospital discharge, depression, anxiety and PTSD occurred significantly more often among women compared to men [7]. On the other hand, meta-analysis of 31 studies including more than 5,000 individuals with SARS-CoV-2 infection did not show significant differences between women and men related to the prevalence of depression and anxiety [8]. A cross-sectional study of 387 patients with COVID-19 in China who completed anonymous online questionnaires upon hospital discharge showed that higher level of education and patient-perceived severity of illness but not sex were predictors of symptoms of anxiety, depression or insomnia [9]. A recent prospective multicenter study in the UK encompassing more than 2,000 individuals discharged from hospital after SARS-CoV-2 infection revealed instead that sleep disturbances affected most of the participants (62%) and were associated with dyspnea as well as anxiety and muscle weakness [10].

Moreover, it is unclear which ESDs exactly affect quality of life at work (QWL). A systematic analysis of the Global Burden of Disease, which was recently published in *The Lancet*, highlighted the importance of this issue, indicating that in 2021 COVID-19, including residual symptoms in the course of long COVID, was responsible for the largest number of disability-adjusted life years worldwide [11]. However, to date, only some papers showed decreased satisfaction in employment after COVID-19 [12], and most of them focused on overall quality of life [13]. Meanwhile, in a group of over 15,000 respondents participating in an American online cohort study, the presence of long COVID symptoms increased the risk of unemployment by almost 1.5 times [14]. Moreover, long COVID reduced the chance of working full-time by 27%, which was mainly associated with brain fog symptoms or memory impairment [14]. In turn, our research group showed that even among COVID-19 outpatients, in the period of more than 12 weeks since the onset of infection, just over half of the participants reported

decreased quality of life at work, which, apart from age, was associated with brain fog symptoms [15]. However, the prospective multicenter Dutch CO-FLOW study revealed that only 69% of patients returned to full-time job one year after hospitalization due to COVID-19, which significantly reduced the quality of life in all domains, including mental health [16]. Therefore, it is necessary to assess ESDs also in the context of brain fog symptoms and quality of life at work.

The prognostic role of laboratory parameters, such as hemoglobin concentration in the acute phase of SARS-CoV-2 infection, is also unclear in relation to development of ESDs within the next few months following onset of disease. So far, it was known that anemia in patients with COVID-19 increased more than twofold the risk of in-hospital mortality and severe course of infection [17]. On the contrary, an Italian study of more than 200 individuals hospitalized due to SARS-CoV-2 infection showed that the presence of anemia affected neither transfer to the intensive care unit (ICU) nor survival within one month since hospital admission [18]. In previous studies, anemia and hyperferritinemia were found more often among cases with severe COVID-19 [19], and different pathophysiological mechanisms, including hemolysis, were postulated [20]. Interestingly, a prospective study involving 362 people showed that one and five months after SARS-CoV-2 infection, anemia was the most common abnormality in blood laboratory tests, both among outpatients and those previously hospitalized due to COVID-19 [21]. Thus, it seems reasonable to further investigate the prognostic role of anemia in the long term [22].

Therefore, the aim of the presented study was to evaluate an incidence of ESDs among patients previously hospitalized due to COVID-19, identify their possible predictors, and understand their influence on co-existing brain fog symptoms (BFS) and quality of life at work (QWL).

Methods

Based on previously validated short screening questionnaires for mood and anxiety disorders (*Patient Health Questionnaire-2* [23] and K6 [24]), as well as for sleeping disturbances [25, 26], we created a short six-point questionnaire for ESDs which was further validated in a group of 70 people, including neurologists, other physicians, physiotherapists, speech therapists, and neuropsychologists [15]. Individuals were retrospectively asked if they experienced: (1) sadness, (2) anxiety, (3) restlessness, (4) insomnia, (5) excessive daytime sleepiness, and (6) nightmares. Participants once only and retrospectively filled out questionnaire, assessing the presence and intensity of the above-mentioned ESDs in four time periods, i.e., before COVID-19, within 0–4, 4–12, and >12 weeks post-infection, using a 4-point Likert scale where 0, 1, 2 or 3 denoted no, mild, moderate, or severe symptom, respectively. Additionally, as described previously, patients evaluated the presence of eight brain fog symptoms through validated BF-COVID questionnaire and reported their QWL with the use of a 4-point Likert scale, with 0, 1, 2 or 3 meaning no, mild, moderate, or severe impairment at work,

respectively [15]. Details on the psychometric analysis of the BF-COVID questionnaire in Polish conditions can be found in the authors' previous work [15].

Paper version of ESD and BF-COVID questionnaires was completed between April and August 2021 by participants who attended the post-COVID ambulatory in the University Hospital in Krakow. Additionally, online links posted on Facebook or sent via mass email to University Hospital employees allowed for anonymous electronic questionnaires collection. After receiving these questionnaires, matching with electronic hospital database was performed in order to gather further data regarding age, sex, concomitant diseases, pre-admission therapy, results of the first laboratory tests since hospital admission, and date of confirmed SARS-CoV-2 infection.

Psychometric analysis of the ESD questionnaire

We performed an exploratory factor analysis (EFA) and evaluated reliability. Initially, we excluded variables with an intercorrelation coefficient ≥0.8 based on the correlation matrix. Following this, we assessed sample adequacy using Bartlett's sphericity test and the Kaiser-Meyer-Olkin (KMO) measure. With Bartlett's p-value <0.05 and KMO >0.5, we conducted an EFA with orthogonal rotation to explore domain structure. The number of items was determined via scree plot analysis and the Eigenvalue criterion, with a factor loading cut-off 0.5. Ultimately, we discerned three distinct domains. We assessed the internal consistency of the ESD questionnaire using Cronbach's α, considering values ≥0.70 as acceptable [27, 28].

Material

Inclusion criteria encompassed the following: age of 18 or more years, period of more than 3 months from onset of SARS-CoV-2 infection confirmed previously by detection of viral RNA with reverse transcription polymerase chain reaction from nasopharyngeal swab, hospitalization due to COVID-19 during acute phase of disease, and the ability to write and read. Excluded were individuals who required ICU intervention. After further exclusion of ESD and BF-COVID questionnaires with incomplete data, information regarding 181 participants was included in the analysis.

The severity of comorbidities was classified into three grades based on Charlson Comorbidity Index (CCI) as follows: mild (scores of 1–2), moderate (scores of 3–4) and severe (scores of 5 or higher) [29].

Finally, the study involved 181 hospitalized patients, with a mean age of 56.02 ± 13.02 years. Of these, 37.02% (n = 67) were women (Table 1).

Patient consent and ethics approval

Current study was carried out in accordance with the Declaration of Helsinki as part of the CRACoV-HHS project (CRAcow in CoVid pandemics – Home, Hospital,

and Staff). We received approval from the Jagiellonian University Bioethics Committee. Individuals attending post-COVID ambulatory in the University Hospital in Krakow signed written informed consent before completing paper version of ESD and BF-COVID questionnaires. In accordance with Polish law, no written consent was necessary to obtain from individuals filling out online version of ESD and BF-COVID questionnaires, however, full information on the study purpose was introduced to them [15, 30].

Statistical analyses

STATISTICA 13.0 software was employed for all statistical analyses. Qualitative variables were reported as numbers and percentages. Comparison of these variables involved using the χ^2 and Cochran's Q tests for dependent variables when applicable. Quantitative variables were presented as mean ± standard deviation, median and interquartile range (IQR) contingent upon the normality of distribution, as assessed by the Shapiro-Wilk test. The two groups were compared using either Student's t-test or the Mann-Whitney U test as appropriate. Kruskal-Wallis test and Friedman's ANOVA were employed for comparisons involving more than two groups, followed by Dunn's post hoc test when applicable.

Variables demonstrating an association with the outcome in the univariate model (with a significance level of p <0.05 and a correlation coefficient with other independent variables of r <0.6) were integrated into the multivariable models. The multivariable models were constructed as follows: (1) for "hemoglobin," including age, female sex, NT-proBNP, D-dimers, chronic heart failure, depression, and antidepressant use; (2) for "pre-existing ESDs," considering age, female sex and hemoglobin; (3) for "new-onset ESDs," involving age, female sex, hemoglobin, hypercholesterolemia, smoking; (4)–(6) for "the deterioration of quality of life at work over 12 weeks post-COVID," comprising [Model A] age, female sex, new and pre-existing ESDs, obesity, and platelets; [Model B] considering Model A and brain fog symptoms within any time interval after COVID-19; [Model C] age, female sex and elements of ESDs such as sadness, anxiety, restlessness, insomnia, excessive daytime sleepiness, and nightmares. We defined a decline in the QWL as a reduction of at least one level on the 4-point Likert scale in comparison to the pre-COVID measurement [15].

All models were developed through a stepwise logistic regression using backward elimination, and the findings were expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Furthermore, we conducted model calibration utilizing the Hosmer-Lemeshow test, and the appropriateness of the models was assessed through the Akaike Information Criterion. We employed receiver operating characteristic curves to gauge the models' discriminatory capacity. Pairwise comparisons were subjected to the Bonferroni correction, considering a significance level of l<0.017 (refer to Tables 1 and 3). Other comparisons used a p-value threshold below 0.05.

Results

Psychometric evaluation of the ESD questionnaire

The final version of the questionnaire was administered to 181 participants to assess its psychometric properties. Two-tailed correlation scores for all items were acceptable (<0.8). The dataset proved suitable for EFA, supported by a KMO value of 0.799, and the Bartlett's sphericity test remained significant ($\chi^2 = 4699$; $df = 276$; p-value <0.001). Three distinct domains emerged from the analysis: "Mental Health" and "Sleep Quality I and II," which explained 59.58% of the total variance (Supplementary Table). Cronbach's alpha of 0.906 indicated satisfactory internal consistency of the ESD questionnaire.

Initial characteristics

Patients in the acute phase of COVID-19 had a mean hospitalization duration of 11.23 ± 5.25 days, and the mean follow-up from the initial positive swab for SARS-CoV-2 was 6.68 ± 3.50 months. The mean Charlson Comorbidity Index (CCI) scores of 1.27 ± 1.10 indicated low comorbidity. Over half of patients had CCI scores of 0 or 1 ($n = 100$; 55.25%), with the most common comorbidities being hypertension, obesity and smoking (Table 1). Antidepressants were administered before the disease in 11.6% ($n = 21$) of cases, benzodiazepines in 3.32% ($n = 6$) and neuroleptics in 2.21% ($n = 4$). Upon admission, the average Modified Early Warning Score (MEWS) was 1.28 ± 0.57 points, and nearly 8 out of 10 patients had a MEWS score of 1 point, indicating low-to-moderate risk; however, only 12.71% ($n = 23$) of patients did not require oxygen therapy; among those needing it, 124 patients used a nasal cannula, and 32 used a simple face mask. None of the patients required ICU treatment.

Table 1. **Baseline characteristics**

	Emotional and sleep disturbances			
	No (*n* = 50)	**Yes (*n* = 129)**		***p*-value**
		pre-existing (*n*=53)	**post-COVID (*n* = 76)**	
Population characteristics				
Age (years)	58 (45–65)	58 (44–69)	57 (47–64)	0.910
Female sex, n (%)	10 (20.00)	26 (49.06)*	31 (40.79)*	0.007
Hypertension, n (%)	21 (42.00)	27 (50.94)	29 (38.16)	0.347
Hypercholesterolemia, n (%)	15 (30.00)	10 (18.87)	11 (14.47)*	0.101
Diabetes mellitus, n (%)	11 (22.00)	6 (11.32)	12 (15.79)	0.336
Obesity, n (%)	22 (44.00)	17 (32.08)	26 (34.21)	0.399
Smoking, n (%)	18 (36.00)	19 (35.85)	16 (21.05)	0.093
CHF, n (%)	2 (4.35)	2 (4.17)	3 (4.23)	0.999
IHD, n (%)	5 (10.00)	6 (11.32)	5 (6.58)	0.619
Atrial fibrillation, n (%)	4 (8.00)	3 (5.66)	5 (6.58)	0.892
Previous stroke	2 (4.00)	3 (5.66)	4 (5.26)	0.921
Asthma or COPD, n (%)	4 (8.00)	5 (9.43)	9 (11.84)	0.769
CKD grade ≥3, n (%)	2 (4.00)	0 (0.00)	2 (2.63)	0.372
Depression, n (%)	3 (6.00)	2 (13.21)	9 (11.84)	0.411
Pre-admission therapy				
Anticoagulants, n (%)	5 (10.00)	4 (7.55)	4 (5.26)	0.889
Antidepressant, n (%)	3 (6.00)	9 (16.98)	9 (11.84)	0.223
Benzodiazepine, n (%)	1 (2.00)	2 (3.77)	1 (1.32)	0.644
Neuroleptics, n (%)	1 (2.00)	2 (3.77)	3 (3.95)	0.821
Symptoms of COVID-19 at the time of admission				
Fever, n (%)	42 (84.00)	46 (86.79)	62 (81.58)	0.731
Cough, n (%)	38 (76.00)	45 (84.91)	66 (86.84)	0.873
Dyspnea, n (%)	32 (64.00)	35 (66.04)	52 (68.42)	0.260
Gastrointestinal, n (%)	17 (34.00)	16 (30.19)	29 (38.16)	0.642
Anosmia, n (%)	10 (20.00)	11 (20.75)	14 (18.42)	0.943
The severity of COVID-19 at the time of admission				
MEWS score (mean ± SD)	1.34 ± 0.69	1.25 ± 0.44	1.28 ± 0.58	
Oxygen therapy, n (%)	49 (88.00)	36 (86.79)	68 (89.47)	0.954
Nasal cannula	31 (62.00)	35 (66.04)	56 (73.68)	0.085
Simple face mask	11 (22.00)	11 (20.75)	12 (15.79)	

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Laboratory analyses				
Hemoglobin (g/L)	14.4 (13.0–15.2)	13.3 (12.5–14.0)*	13.3 (12.4–14.3)*	0.019
Anemia	10 (20.00)	10 (18.87)	24 (31.58)	0.173
PLT (x10^9/L)	185 (139–271)	212 (162–291)	191 (147–271)	0.265
CRP (mg/L)	69 (37–110)	78 (37–126)	75 (33–107)	0.864
D-dimers (mg/L)	0.83 (0.54–1.17)	0.77 (0.45–1.38)	0.83 (0.55–1.27)	0.932
Hs-cTn I (ng/L)	6.7 (3.2–11.4)	6.1 (4.2–13.7)	2.8 (4.9–11.8)	0.412
NT-proBNP (pg/ml)	137 (57–251)	145 (70–372)	138 (60–401)	0.731

Data are presented as numbers (*n*) and percentages (%), median and interquartile range, and mean ± standard deviation, as appropriate. The Bonferroni corrected *p*-value <0.017 when compared to no ESD (*) and preexisting ESD (#). COPD – chronic obstructive pulmonary disease; CRP – C-reactive protein; COVID-19 – coronavirus disease of 2019; hs-Tn I – high-sensitivity cardiac troponin I; CHF – chronic heart failure; CKD – chronic kidney disease; ESD – emotional and sleep disturbances; IHD – ischemic heart disease; MEWS – Modified Early Warning Score; NT-proBNP – N-terminal pro–B-type natriuretic peptide; and PLT – platelets count.

Emotional and sleep disturbances before and after COVID-19

Before the onset of COVID-19, 30.38% (*n* = 55) of patients reported any ESD. In total, 129 patients (71.27%) reported any ESD during follow-up, including 40.33% with new-onset ESDs and 53 (29.28%) with pre-existing stable or exacerbated symptoms of ESDs after COVID-19. Interestingly, two patients reported resolution of pre-existing ESDs after SARS-CoV-2 infection.

COVID-19 demonstrated an association with a 1.6 to 2.2-fold increase in the incidence of any ESD within 4, 4–12, and beyond 12 weeks (66.85% [*n* = 121], 60.77% [*n* = 110] and 50.28% [*n* = 91], respectively; *p* <0.001 for all intervals; Table 2). The most prevalent ESDs of any severity were restlessness and insomnia, followed by sadness and anxiety, with only partial resolution observed after >12 weeks since the onset of the disease. Patients reported normalization in excessive daytime sleepiness within less than 4 weeks and nightmares within 4–12 weeks since the onset of infection.

Table 2. **Elements of the emotional and sleep disturbances (ESDs) before and after COVID-19**

Emotional and sleep disturbances	Before COVID-19 (*n* = 181)	After COVID-19					
		0–4 weeks (*n* = 181)		4–12 weeks (*n* = 180)		>12 weeks (*n* = 178)	
	n (%)	*n* (%)	*p*-value vs. before COVID-19	*n* (%)	*p*-value vs. before COVID-19	*n* (%)	*p*-value vs. before COVID-19
1. Sadness							
Mild	15 (8.23)	34 (18.78)	<0.001	29 (16.11)	<0.001	25 (14.04)	<0.014
Moderate	2 (1.10)	15 (8.23)		9 (5.00)		8 (4.59)	
Severe	–	13 (7.18)		7 (3.89)		3 (1.69)	
2. Anxiety							
Mild	15 (8.28)	27 (14.92)	<0.001	31 (17.22)	<0.001	24 (13.49)	<0.025
Moderate	4 (2.21)	23 (12.71)		13 (7.22)		8 (4.50)	
Severe	–	14 (7.73)		7 (3.89)		3 (1.69)	
3. Restlessness							
Mild	21 (11.60)	52 (28.73)	<0.001	53 (29.44)	<0.001	35 (19.66)	<0.005
Moderate	5 (2.76)	25 (13.81)		15 (8.33)		13 (7.31)	
Severe	–	16 (8.83)		8 (4.44)		4 (2.25)	
4. Insomnia							
Mild	19 (10.49)	43 (23.76)	<0.001	44 (24.44)	<0.001	31 (17.41)	<0.011
Moderate	6 (3.31)	18 (9.95)		11 (6.11)		9 (5.06)	
Severe	2 (1.11)	15 (8.23)		10 (5.56)		10 (5.62)	
5. Excessive daytime sleepiness							
Mild	17 (9.39)	22 (12.15)	<0.014	20 (11.11)	<0.074	21 (11.80)	<0.161
Moderate	5 (2.76)	11 (6.08)		17 (9.44)		9 (5.06)	
Severe	1 (0.55)	10 (5.52)		2 (1.11)		2 (1.12)	
6. Nightmares							
Mild	10 (5.52)	19 (10.50)	<0.001	22 (12.22)	<0.001	16 (8.99)	<0.071
Moderate	1 (0.55)	5 (2.76)		2 (1.11)		1 (0.56)	
Severe	–	4 (2.21)		–		1 (0.56)	

The data is displayed as numbers (n) and percentages (%), and they were evaluated using the Cochran's *Q* test.

Severe ESDs were infrequent before COVID-19 ($n = 3$; 1.66%), but following the onset of the disease, the incidence increased more than 11-fold – to 18.78% ($n = 34$) of patients. The exacerbation of restlessness, insomnia, excessive daytime sleepiness, sadness, and anxiety within four weeks primarily drove this increase.

Patients who experienced any ESD after COVID-19 were more frequently women and had a lower prevalence of hypercholesterolemia and lower hemoglobin levels compared with those with no symptoms (Table 1). There was no difference in baseline characteristics between groups with pre-existing and post-COVID ESDs.

Hemoglobin levels and the association with emotional and sleep disturbances

The median and mean hemoglobin levels were 13.4 (12.5–14.4) and 13.43 ± 1.66 g/L, respectively, and 24.31% ($n = 44$) of patients had hemoglobin levels measured upon admission below the reference range (i.e., <12 g/L in women and <13 g/L in men).

Patients with hemoglobin below the lower reference limit were older (61 [53–71] vs. 56 [44–64] years; $p = 0.005$), had elevated NT-proBNP levels (302 [131–674] vs. 123 [59–236] pg/ml; $p \leq 0.001$), increased D-dimers (1.04 [0.62–1.68] vs. 0.76 [0.47–1.12] mg/L; $p = 0.008$), and a higher prevalence of chronic heart failure (12.82% vs. 1.57%; $p = 0.002$), depression (20.45% vs. 7.30%; $p = 0.013$), and antidepressant use (20.45% vs. 8.76%; $p = 0.035$), compared to patients with hemoglobin within the reference limit.

Independent predictors of hemoglobin below the lower reference limit included female sex (OR = 2.25; 95% CI: 1.01–5.03), chronic heart failure (OR = 8.99; 95% CI: 1.45–55.80), D-dimers (OR = 1.10; 95% CI: 1.01–1.20 per mg/L), and NT-proBNP (OR = 1.01; 95% CI: 1.00–1.01 per pg/ml; $p = 0.001$).

Patients in the first quartile of hemoglobin measured on admission (<12.5 g/dl) exhibited a higher incidence of ESDs compared to the highest hemoglobin quartile (79.55% vs. 50.98%; OR = 3.73; 95% CI: 1.50–9.34; $p = 0.004$). Additionally, the lowest hemoglobin quartile was associated with ESDs persisting beyond 12 weeks from COVID-19 diagnosis (63.64% vs. 33.33%; OR = 3.50; 95% CI: 1.50–8.16; $p = 0.003$ vs. the fourth quartile).

In the multivariable model, adjusted for age and sex, pre-existing ESDs before COVID-19 were associated with hemoglobin levels (OR = 0.71; 95% CI: 0.53–0.97 per g/L) and female sex (OR 2.70; 95% CI: 1.05–6.95). Notably, new-onset ESDs after COVID-19 were solely predicted by hemoglobin levels (OR = 0.64; 95% CI: 0.50–0.80 per g/L; Table 3).

Table 3. **Independent predictors of emotional and sleep disturbances in patients hospitalized due to COVID-19**

Pre–existing ESDs					
Univariable model	OR (95% CI)	p–value	Multivariable model	OR (95% CI)	p–value
Age (per 10 years)	1.02 (0.78–1.34)	0.866	Age (per 10 years)	0.92 (0.68–1.24)	0.580
Female sex	3.85 (1.60–9.26)	0.003	Female sex	2.70 (1.05–6.95)	0.039
Hemoglobin (per g/L)	0.63 (0.46–0.85)	0.003	Hemoglobin (per g/L)	0.71 (0.53–0.97)	0.030
			AIC	133.12	
			AUC (95% CI)	0.713 (0.611–0.815)	
			The Hosmer–Lemeshow test p–value	0.412	
New–onset ESDs					
Univariable model	OR (95% CI)	p–value	Multivariable model	OR (95% CI)	p–value
Age (per 10 years)	0.97 (0.74–1.28)	0.818	Age (per 10 years)	1.03 (0.76–1.40)	0.865
Female sex	2.76 (1.20–6.32)	0.017	Female sex	1.71 (0.63–4.60)	0.290
Hypercholesterolemia Smoking	0.40 (0.16–0.95) 0.47 (0.21–1.05)	0.039 0.067	Hemoglobin (per g/L)	0.64 (0.50–0.80)	0.001
Hemoglobin (per g/L)	0.75 (0.50–0.84)	0.001			
			AIC	160.63	
			AUC (95% CI) The Hosmer–Lemeshow test P–value	0.665 (0.565–0.765) 0.637	

Models were adjusted for age and sex. Please refer to Table 1 for abbreviations: AIC – Akaike information criterion; AUC – the area under the curve; CI – the confidence interval; and OR – the odds ratio.

Emotional and sleep disturbances and their association with brain fog symptoms

In individuals without reported symptoms of ESDs, the occurrence of brain fog symptoms (BFS) was low, not surpassing 25%. Interestingly, in the subgroup with pre-existing ESDs before COVID-19, there was no difference in the incidence of BFS when compared to the group without ESDs, as indicated in Table 4. However, the onset of SARS-CoV-2 infection was linked to a 2.3-fold, 2.2-fold and 1.9-fold increase in

BFS within 4 weeks, 4–12 weeks, and beyond 12 weeks post-COVID, respectively, in the ESDs group (Figure 1A–D).

Table 4. **The association between emotional and sleep disturbances, symptoms of brain fog and the impact on work-related quality of life in patients hospitalized due to COVID-19**

	Emotional and sleep disturbances			
	No (n = 50)	Yes (n = 129)		p-value
		pre-existing (n = 53)	new-onset (n = 76)	
Brain fog symptoms (BFS) within any time interval	12 (24.00)	43 (81.13)*	57 (75.00)*	<0.001
BFS before COVID-19	9 (18.00)	18 (33.96)	11 (14.47)#	0.023
BFS <4 weeks after COVID-19	11 (22.00)	41 (77.36)*	53 (69.74)*	<0.001
BFS 4–12 weeks after COVID-19	11 (22.00)	38 (73.08)*	47 (61.84)*	<0.001
BFS >12 weeks after COVID-19	12 (24.00)	34 (65.38)*	42 (56.76)*	<0.001
Deterioration of quality of life at work (dQWL)				
dQWL <4 weeks after COVID-19	3 (6.00)	28 (52.83)*	34 (44.74)*	<0.001
dQWL 4-12 weeks after COVID-19	2 (4.00)	19 (36.54)*	32 (42.11)*	<0.001
dQWL >12 weeks after COVID-19	1 (2.00)	16 (30.77)*	26 (35.14)*	<0.001

Data are presented as numbers (n) and percentages (%). The Bonferroni corrected *p*-value <0.017 when compared to no ESDs (*) and pre-existing ESDs (#).

In the subset of individuals experiencing new-onset ESDs, COVID-19 was linked to a 4.8–fold, 4.3-fold and 3.9-fold increase in brain fog symptoms (BFS) within 4, 4–12, and beyond 12 weeks post-infection, respectively. Despite the greater magnitude of increase in BFS within this group, the incidence of BFS did not differ between subgroups with new-onset and pre-existing ESDs in the abovementioned intervals (Table 4 and Figure 1A-D).

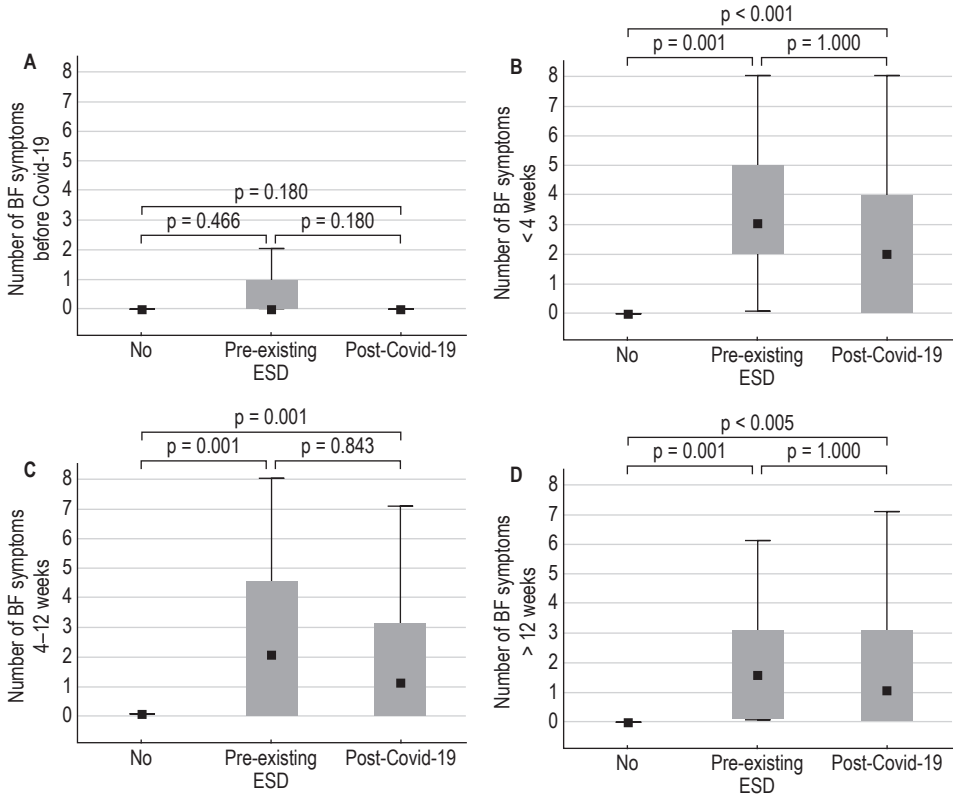


Figure 1. **The association between emotional and sleep disturbances and the quantity of brain fog symptoms during different phases after COVID-19: (A) before COVID-19, (B) acute phase (less than 4 weeks), (C) subacute phase (4–12 weeks), and (D) chronic phase (more than 12 weeks)**

The information was analyzed using the Kruskal–Wallis test and a multiple comparisons test, and the results are presented as a median, interquartile range, as well as the minimum and maximum values.

Quality of life at work – associations with emotional and sleep disturbances and brain fog symptoms

Individuals without ESDs exhibited a minimal incidence of deterioration in quality of life at work (QWL) after COVID-19, at less than 10% (see Table 4). In contrast, approximately half of individuals with ESDs reported decreased QWL within four weeks after SARS-CoV-2 infection, with no notable difference between subgroups with new-onset and pre-existing ESDs. Beyond 12 weeks from COVID-19, QWL impairment was at least 15-fold more frequent in patients with any ESD (Table 4).

We established three models to examine the complex interplay among QWL, ESDs, and elements of brain fog post-COVID. Model A centered on ESDs, while model B incorporated BFS. Model C specifically targeted the components of ESDs contributing to the deterioration of QWL.

The decline in QWL beyond 12 weeks post-COVID onset was independently predicted by age, female sex, and both pre-existing and new-onset ESDs (Model A, in Table 5). Model B expanded this list to include BFS, obesity and platelet count. When investigating the components of ESDs in Model C, four elements, i.e., sadness (Question 1.1), restlessness (Question 1.3), insomnia (Question 1.4), and excessive daytime sleepiness (Question 1.5), alongside age, were identified as predictors of a decrease in QWL (Table 5).

Table 5. **Independent predictors of the deterioration of quality of life at work (QWL) >12 weeks in patients hospitalized due to COVID-19. Model A relies on emotional and sleep disturbances (ESDs), while model B incorporates brain fog symptoms. Meanwhile, model C identifies the specific components of ESDs that contribute to the impairment of QWL**

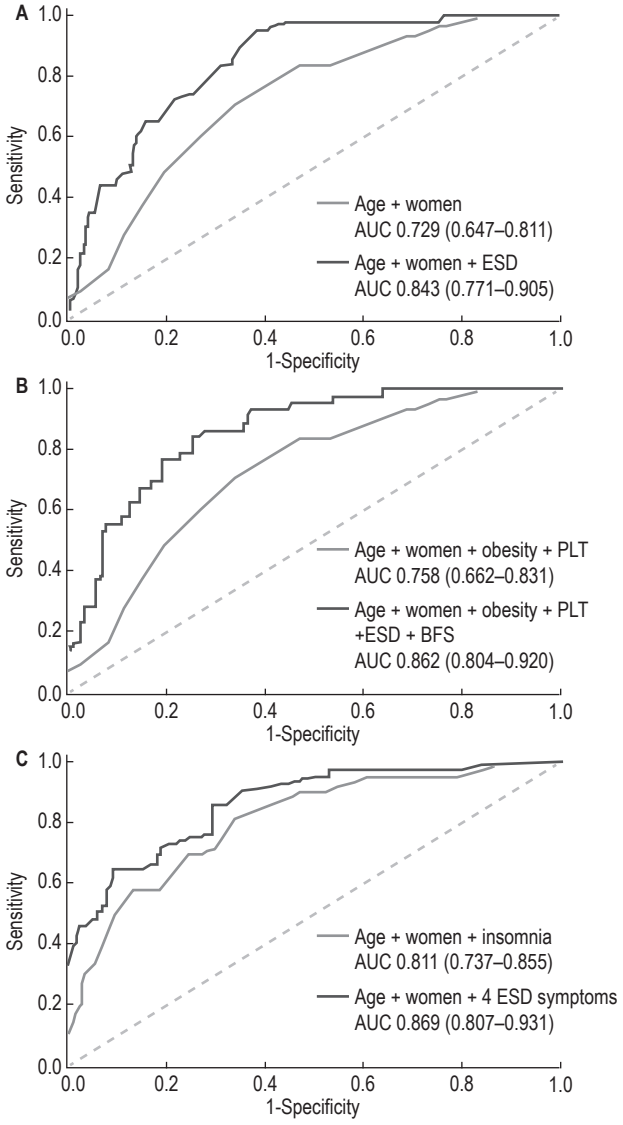
Deterioration of quality of life at work >12 weeks after COVID-19					
Univariable model model A	**OR (95% CI)**	***p*-value**	**Multivariable model A**	**OR (95% CI)**	***p*–value**
Age (per 10 years)	0.63 (0.48–0.82)	<0.001	Age (per 10 years)	0.62 (0.37–0.73)	<0.001
Female sex	2.32 (1.15–4.67)	0.019	Female sex	3.47 (1.40–8.56)	0.007
ESDs			ESDs		
Pre–existing	21.77 (2.76–171.8)	0.004	Pre–existing	21.58 (2.57–181.30)	0.005
New onset	26.5 (3.46–203.4)	0.002	New onset	30.88 (3.85–247.90)	0.001
Obesity	1.97 (0.98–3.97)	0.056	–	–	
PLT (per 1x10^9/L)	1.00 (1.00–1.01)	0.025	–	–	
			AIC	154.10	
			AUC (95% CI)	0.843 (0.771–0.905)	
			The Hosmer–Lemeshow test p–value	0.535	
Univariable model model B	**OR (95% CI)**	***p*–value**	**Multivariable model B**	**OR (95% CI)**	***p*–value**
Age (per 10 years)	0.63 (0.48–0.82)	<0.001	Age (per 10 years)	0.52 (0.37–0.74)	<0.001
Female sex	2.32 (1.15–4.67)	0.019	Female sex	3.39 (1.34–8.671)	0.010
ESDs			ESDs		
Pre–existing	21.77 (2.76–171.8)	0.004	Pre–existing	10.60 (1.18–95.19)	0.004
New onset	26.5 (3.46–203.4)	0.002	New onset	17.90 (2.11–151.55)	0.008

table continued on the next page

Brain fog symptoms within any time interval	6.65 (2.47–17.93)	<0.001	Brain fog symptoms within any time interval	3.56 (1.10–11.55)	0.034
Obesity	1.97 (0.98–3.97)	0.056	Obesity	3.22 (1.29–8.03)	0.012
PLT (per 1x10^9/L)	1.00 (1.00–1.01)	0.025	PLT (per 1x10^9/L)	1.01 (1.00–1.01)	0.039
Hemoglobin (g/L)	0.88 (0.72–1.09)	0.241			
			AIC	150.12	
			AUC (95% CI)	0.862 (0.804–0.920)	
			The Hosmer–Lemeshow test p–value	0.979	
Univariable model C	**OR (95% CI)**	***p*–value**	**Multivariable model C**	**OR (95% CI)**	***p*–value**
Age (per 10 years)	0.63 (0.48–0.82)	<0.001	Age (per 10 years)	0.42 (0.28–0.63)	<0.001
Female sex	2.32 (1.15–4.67)	0.019	Female sex	1.94 (0.76–4.98)	0.167
1. Sadness	7.64 (3.42–17.06)	<0.001	1. Sadness	3.77 (1.24–11.50)	0.002
2. Anxiety	5.00 (2.27–11.02)	0.001	–	–	
3. Restlessness	5.56 (2.66–11.62)	<0.001	3. Restlessness	2.74 (1.02–7.40)	0.046
4. Insomnia	4.00 (1.93–8.30)	<0.001	4. Insomnia	6.32 (2.26–17.65)	<0.001
5. Excessive daytime sleepiness	5.22 (2.74–14.14)	<0.001	5. Excessive daytime sleepiness	3.32 (1.13–9.70)	0.028
6. Nightmares	6.29 (2.58–17.50)	<0.001	–	–	
			AIC	141.15	
			AUC (95% CI) The Hosmer–Lemeshow test p–value	0.869 (0.807–0.931) 0.381	

Please refer to Table 1 for abbreviations.

The aforementioned models, incorporating variables such as self-reported ESDs, as well as BFS, demonstrated robust discriminatory capabilities in assessing the QWL post-COVID. The median area under the curve (AUC) reached up to 0.869 (95% CI: 0.807–0.931), surpassing models relying solely on demographic and other clinical variables, as detailed in Table 5 and Figure 2A–C.



Model A is based on emotional and sleep disturbances (ESD), whereas model B includes brain fog symptoms. In contrast, model C aims to pinpoint the particular elements within ESD that lead to the decline in QWL. The models that incorporated one or more ESD demonstrated a greater area under the ROC curves in comparison to models that exclusively depended on age and sex as predictors.

Figure 2. **Receiver operating characteristic (ROC) curves of the models used to forecast the decline in quality of life at work (QWL) during the chronic phase following COVID-19**

Data corroborating the findings of this study can be obtained from the corresponding author upon reasonable request.

Discussion of the results

The main findings of this study are: (1) Most patients with COVID-19 experience emotional and sleep disturbances (ESDs) during follow-up, which are predicted by

hemoglobin levels; (2) ESDs increase the risk of concomitant brain fog symptoms (BFS); (3) ESDs, especially sadness, restlessness, insomnia, and excessive daytime sleepiness, strongly affect quality of life at work (QWL) >12 weeks post-COVID.

Our study demonstrated that presence of anemia during an acute phase of COVID-19 among patients hospitalized at non-ICU wards independently predicted the risk of developing or aggravating ESDs within six months of follow-up after an initial infection. This risk was increased by approximately one-third, both in individuals with and without pre-existing ESDs. The results of our research stayed in line with a prospective Austrian study of 108 participants with SARS-CoV-2 infection in whom persistent anemia and alterations in iron homeostasis were associated with reduced capacity to cope with stress as measured with *Brief Resilient Coping Scale* [31]. A recent study involving non-hospitalized patients with COVID-19 with age group similar to ours also confirmed the prognostic role of anemia as its presence, attributed to nutritional deficiency, doubled the risk of post-COVID sequelae [32]. The etiology of so called 'long COVID' is likely multifactorial with hyperferritinemia and oxidative stress as potential contributors [33]; additionally, decreased levels of hemoglobin could also play a significant role in developing weakness and fatigue after an acute phase of infection [34]. Interestingly, previous studies also revealed significant associations between anemia and depression [35] as well as with insomnia [36]. Therefore, the results of our study might be viewed as potentially pathophysiological hypothesis-generating as recently a correlation between long COVID and impaired function of erythrocytes was suggested; therefore, diminished supply of oxygen could contribute to chronic fatigue syndrome and anemia [37]. Additionally, hypoxia may lead to neuronal damage; however, it seems that pathophysiology of neurological and psychiatric complications after COVID-19 is multidirectional with significant role of both inflammatory process [38] and renin-angiotensin-aldosterone system [39].

Our study also confirmed significant association between ESDs and BFS within 6 months after the onset of SARS-CoV-2 infection. Our results resembled findings from a large meta-analysis published in 2022, where female sex as well as depressive and anxiety disorders increased the risk of suffering from persistent fatigue and cognitive disturbances after COVID-19 [40]. Furthermore, as shown in a prospective study of nearly 1,300 patients discharged from 21 hospitals in Los Angeles, USA, the presence of depressive disorder or cognitive difficulties increased the risk of long COVID at 60 to 90 days of follow-up 1.72 and 1.81 times, respectively [41]. On the other hand, in a recent Australian cohort, long COVID strongly predicted the occurrence of neuropsychiatric symptoms following an acute phase of infection, including fatigue and depression, and decreasing quality of life [42]. However, conclusions similar to ours were obtained in a recent Chinese online questionnaire study involving more than 5,000 mental health professionals, where participants with post-COVID sequelae in comparison to those without such residual symptoms significantly more often experienced depression, anxiety, insomnia, and suicidality [43]. Our study also revealed that symptoms such as sadness, anxiety, restlessness, and insomnia were reported by

participants not only in the acute phase of infection but also persisted for more than 12 weeks post-COVID. Our results are in accordance with a systematic review of 18 studies encompassing more than 10,000 patients with SARS-CoV-2 infection, in which prevalence of anxiety, depression and insomnia was still substantial even within more than 6 months after the onset of COVID-19 [44]. Interestingly, a recent study of Dutch P4O2 consortium revealed three distinct clusters of long COVID, of which the most common (44%) was the variant predominant among females with a median of four symptoms of different categories, including fatigue, neurological and respiratory symptoms [45]. However, in a cohort of 2,300 beneficiaries of the American Military Healthcare System, with predominant male subgroup (65%) and evaluated with detailed neuropsychological questionnaires after a mean of 2.5 months since the first positive SARS-CoV-2 test, fatigue, cognitive impairment and depression were also 2.07, 1.64 and 1.44 times more common in comparison to healthy individuals, respectively [46]. Thus, a significant proportion of patients following SARS-CoV-2 infection still suffers from both ESDs and symptoms of brain fog.

With the use of our multivariable models, which showed robust discriminatory values, we were able to identify specific components of ESDs such as sadness, restlessness, insomnia, and excessive daytime sleepiness that affected work-related quality of life independently of other variables apart from age. Similarly, in a cross-sectional study of nearly 400 individuals evaluated after at least 12 weeks post-COVID, quality of life was predicted by both depressive and post-COVID symptoms [47]. Previous studies also pointed to bidirectional relationship between insomnia and long COVID, as shown in an international collaborative research involving more than 2,000 participants with SARS-CoV-2 infection, in which patients with pre-existing insomnia had 1.33 times higher risk of long COVID, whereas those with long COVID developed insomnia 2 times more often [48]. In a recent observational prospective study of 1565 Colombian patients with COVID-19, it was shown that within 24 months of follow-up anxiety, depression and insomnia still affected high proportion of survivors (i.e., 17%, 22% and 24%, respectively), and their predictors included initial disease severity and physical comorbidities among others; however, this population was younger than ours (mean age 51.5), with equal sex distribution [49]. On the other hand, excessive daytime sleepiness might be the symptom of previously unrecognized obstructive sleep apnea [50]. Indeed, as shown in our study, obesity perceived as one of the most important risk factors for sleep apnea [51], apart from ESDs, predicted the risk of deterioration in QWL within 12 weeks post-COVID. Thus, an interdisciplinary approach seems reasonable in patients with long COVID in order to adequately diagnose and alleviate residual symptoms after an acute phase of infection. This issue becomes particularly important in the context of the wide spectrum of possible post-COVID complications, affecting cardiovascular system and causing hematological, gastroenterological, endocrine, dermatological, and immunological disturbances, that has been confirmed by the latest research in this field [52, 53]. The most recent data from CONTAIN COVID-19 clinical trial also indicate that within 18 months since hospitalization due

to SARS-CoV-2 infection, patients are twice as likely to experience abnormalities in physical health, including walking, carrying shopping and pain, than in various aspects of mental health, such as mood and thinking disturbances as well as depression and anxiety, which physicians should not forget about in clinical practice [54].

Our research has several important limitations that were addressed in our previously published papers, such as retrospective design, small sample size and reliance on subjective self-reported outcomes with inability to confirm the accuracy of responses [15, 30]. Particularly, patients once only filled out questionnaires when evaluating status before COVID-19 and within specified time periods after infection. Furthermore, no detailed clinical questionnaires for separate evaluation for depression, anxiety and sleep disturbances were used in the current study. Nevertheless, our ESD questionnaire was based on previously validated short screening scales [23–26] and showed satisfactory internal consistency. In addition, presented multivariable models for deterioration of QWL exhibited good AUC values. Besides that, as described previously, QWL was assessed only with a 4-point Likert scale instead of other specially designed questionnaires, however, other studies evaluating quality of life after COVID-19 also employed this scale [15, 55]. Finally, the study did not assess iron deficiency as a potential factor, which could impact the comprehensive understanding of anemia and its associations with ESDs post-COVID.

Conclusions

In conclusion, 71% of patients after SARS-CoV-2 infection report any ESD during follow-up. COVID-19 results in 1.6 to 2.2-fold increase in the incidence of any ESD within more than 12 weeks after the onset of an initial infection. Both pre-existing and new-onset ESDs are predicted by hemoglobin levels in the multivariable model and – only for pre-existing ESDs – additionally by female sex. The SARS-CoV-2 infection increases the risk of developing BFS, especially in the subgroup of patients with new-onset ESDs. Decline in QWL within more than 12 weeks post-COVID is independently predicted by age, female sex and both pre-existing and new-onset ESDs. In our study, we were able to identify specific components of ESDs predicting decrease in QWL after 3 months since the onset of COVID-19, such as sadness, restlessness, insomnia, and excessive daytime sleepiness.

Conflicts of interest: *none declared.*
The last two authors (Leszek Drabik and Marcin Wnuk) contributed equally to this study

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Supplementary Table **1. Exploratory factor analysis of emotional and sleep disturbances survey items**

Factor	Question	Rotated factor loadings	Eigenvalues	Percentage of variance
Mental Health	Sadness	0.677	8.636	35.98
	Anxiety	0.726		
	Restlessness	0.691		
Sleep Quality I	Insomnia	0.537	3.213	13.39
		0.719		
Sleep Quality II	Nightmares	0.733	2.453	10.21
	Excessive daytime sleepiness	0.537		