RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 1, pages: 101–110
DOI: 10.5603/PJNNS.a2023.0015

ISSN: 0028-3843, e-ISSN: 1897-4260

LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

Course of fatigue among patients previously hospitalised due to COVID-19

Iwona Mazurkiewicz[1, 2], Żaneta Chatys-Bogacka[1, 2], Joanna Słowik[3], Magdalena Zdanecka[4], Andżelika Siwiec-Koźlik[5, 6], Agnieszka Słowik[1, 2], Leszek Drabik[7, 8], Marcin Wnuk[1, 2]

[1]Department of Neurology, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Neurology, University Hospital in Krakow, Poland
[3]Department of Periodontology, Preventive Dentistry and Oral Medicine, Institute of Dentistry, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
[4]Clinical Department of Gynaecological Endocrinology and Gynaecology, University Hospital in Krakow, Poland
[5]Department of Rheumatology and Immunology, Jagiellonian University Medical College, Krakow, Poland
[6]Rheumatology and Immunology Clinical Department, University Hospital in Krakow, Poland
[7]Department of Pharmacology, Jagiellonian University Medical College, Krakow, Poland
[8]John Paul II Hospital, Krakow, Poland

ABSTRACT

Introduction. Discrepancies exist regarding the clinical course and prognostic factors for post-COVID fatigue. Therefore, our aim was to assess the timely course of fatigue and its possible predictors in patients previously hospitalised due to SARS-CoV-2 infection.

Material and methods. Patients and employees of the University Hospital in Krakow were assessed with the use of a validated neuropsychological questionnaire. Included were participants aged 18 or more, previously hospitalised due to COVID-19, who completed questionnaires only once > 3 months after the onset of infection. Individuals were retrospectively asked about the presence of eight symptoms of chronic fatigue syndrome at four timepoints: before COVID-19, within 0–4 weeks, 4–12 weeks, and > 12 weeks post-infection.

Results. We enrolled 204 patients [40.2% women, median age 58 (46–66) years] evaluated after a median of 187 (156–220) days from the first positive nasal swab test for SARS-CoV-2. The most common comorbidities were hypertension (44.61%), obesity (36.27%), smoking (28.43%), and hypercholesterolemia (21.08%); none of the patients required mechanical ventilation during hospitalisation. Before COVID-19, 43.62% of patients reported at least one symptom of chronic fatigue. Within 4, 4–12, and > 12 weeks after COVID-19, the prevalence of chronic fatigue was 76.96%, 75.49%, and 66.17%, respectively (all $p < 0.001$). The frequency of chronic fatigue symptoms decreased within > 12 weeks following the onset of infection but did not return to baseline values, except for self-reported lymph node enlargement. In a multivariable linear regression model, the number of fatigue symptoms was predicted by female sex [β 0.25 (0.12; 0.39), $p < 0.001$ and 0.26 (0.13; 0.39), $p < 0.001$ for weeks 0–12 and > 12, respectively], and age [for < 4 weeks, β –0.12 (–0.28; –0.01), $p = 0.029$].

Conclusions. Most patients previously hospitalised due to COVID-19 suffer from fatigue > 12 weeks after infection onset. The presence of fatigue is predicted by female sex and – only for the acute phase — age.

Key words: COVID-19, SARS-CoV-2, fatigue, long COVID, prognosis, middle aged, neurological manifestations

(*Neurol Neurochir Pol 2023; 57 (1): 101–110*)

Address for correspondence: Marcin Wnuk, MD, Department of Neurology, Jagiellonian University Medical College, 2 Jakubowskiego St., 30–688 Krakow, Poland; e-mail: marcin.wnuk@uj.edu.pl

Received: 07.02.2023 Accepted: 16.02.2023 Early publication date: 22.02.2023

Fatigue represents the most common post-acute sequelae of Coronavirus Disease 2019 (COVID-19) [1, 2]. Its prevalence in the acute phase of infection is estimated at more than 60% [3], even among patients who eventually do not develop long COVID syndrome [4]. As shown recently, irrespective of initial improvement, most individuals with a Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection will suffer from fatigue within three months following the onset of disease [5]. This non-specific group of symptoms is more often reported by patients with COVID-19 compared to other viral respiratory infections [6], and its presence significantly deteriorates the perceived quality of life and impairs both leisure activities and work performance [7–10]. It is also noteworthy that post-COVID symptoms, including fatigue, result in a significant burden of healthcare costs, as was recently revealed in a detailed analysis of nearly 30,000 people from the German Nationwide Inpatient Data [11].

Several factors have been shown to predict the presence of fatigue and other post-COVID symptoms [12]; however, discrepancies have been observed regarding the role of demographics, comorbidities and initial severity of infection [13].

For example, a longitudinal observation of 371 patients from India confirmed that predictors of long COVID, with fatigue being its most common self-reported symptom, included pre-existing medical conditions, vaccination status, a higher number of acute COVID-19 symptoms, and the severity of infection, but not sex [14]. In a cross-sectional study of two urban centres in Spain among 360 hospitalised patients assessed via telephone interviews two years after the acute phase of the SARS-CoV-2 infection, it was found that a number of comorbidities and dyspnoea were associated with post-COVID fatigue, but not sex [15]. On the other hand, in another Spanish cohort of mostly non hospitalised patients, post-COVID symptoms, including fatigue, were associated with older age and female sex within six months after the acute phase of infection [16]. A recent comprehensive review listed many possible risk factors for the development of fatigue during long COVID, such as female sex, older age, hospital admission, comorbidities, including chronic pulmonary diseases or migraine, and steroid administration among others [17]. However, other researchers have come to different conclusions, undermining the prognostic role of comorbidities [18] and the initial severity of COVID-19 [19].

When taking into account the course of post-COVID symptoms, including fatigue, this also varies according to the study [20]. For example, in a large online survey of 12,609 registered German stem cell donors who underwent COVID-19, there were no significant differences in the prevalence of post-COVID fatigue between three and 15 months after the initial infection [21]. On the other hand, a Norwegian group showed a tendency for fatigue to improve four months after the onset of COVID-19 [22], whereas Korean researchers observed an increasing fatigue rate between one and six months post-infection [23].

Therefore, we aimed to evaluate the timely course of fatigue and its possible predictors in a sample of patients previously hospitalised due to COVID-19.

Material and methods

Evaluation of post-COVID fatigue

Post-COVID fatigue was assessed with the use of a questionnaire called "The NeuroPsychological Complications of COVID-19" (NP-COVID), created for the purposes of the current study and further validated, as described previously [24]. In brief, patients were retrospectively asked about the presence of the following symptoms: 1) persistent fatigue, not caused by effort, and persisting after rest, 2) sore throat, 3) self-reported lymph node enlargement, 4) myalgia, 5) arthralgia, 6) headache, 7) non-restorative sleep, and 8) prolonged post-exercise fatigue [24]. These symptoms were previously included in a definition of chronic fatigue syndrome (CFS) by the Centres for Disease Control and Prevention in 1994 [25] and, since then, they have been widely used even in newer definitions of the CFS [26]. Moreover, as shown recently, CFS and post-COVID condition share similarities related to fatigue, exhaustion initiating exercise, post-exertional malaise, muscle and joint pain [27, 28].

Questionnaires were completed by patients once only, and the presence of the above-mentioned chronic fatigue symptoms was assessed over four time periods, i.e. before COVID-19, and within 0–4, 4–12, and > 12 weeks since the onset of infection, in accordance with the National Institute for Health and Care Excellence (NICE) guidelines [29, 30].

Patient enrollment

We enrolled patients who fulfilled the following inclusion criteria that were also described previously [24]: age 18 or more years; more than three months since the onset of the SARS-CoV-2 infection; diagnosis of COVID-19 confirmed by detection of viral RNA by reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab; and ability to read and write. Additionally, for the purpose of the current study, we included only patients who had previously required hospitalisation due to SARS-CoV-2 infection.

Patient data was collected from the following sources: post-COVID ambulatory in the University Hospital in Krakow, where participants were encouraged to complete the paper version of the NP-COVID questionnaire, and an online link posted on Facebook, or sent via group e-mail to employees of the University Hospital in Krakow, that encompassed the online version of the questionnaire. Therefore, between April and August 2021, a total of 660 anonymous NP-COVID questionnaires were received. We then excluded questionnaires provided by patients with incomplete data, allowing 204 subjects to be included in the final analysis.

Bioethics and patient consent

We conducted this study within the CRACoV-HHS project (CRAcow in CoVid pandemics — Home, Hospital and Staff) and in accordance with the Declaration of Helsinki. The CRACoV-HHS project received approval of the Jagiellonian University Bioethics Committee. No additional approval from the Bioethics Committee was required since NP-COVID questionnaires were filled out anonymously [24]. Participants who were recruited in the post-COVID ambulatory in the University Hospital in Krakow signed written informed consent before the paper version of the NP-COVID questionnaire was handed to them. In accordance with Polish law, no written consent needed to be obtained from patients who completed the online questionnaire anonymously; however, full information on the aim of the survey was provided.

Statistics

Data was presented as counts and percentages (n, [%]), mean and standard deviations (SD), and median and interquartile ranges (IQR). Continuous variables were checked for normality with the Shapiro-Wilk test. Where the distribution was non-normal, data was compared using the Mann-Whitney test, Kruskal-Wallis test and Friedman's ANOVA, as appropriate. Categorical independent variables were tested with the $\chi 2$ test and Fisher's exact test, while categorical dependent variables were analysed with the Cochran's Q test and the McNemar $\chi 2$ test. We applied Bonferroni correction for pairwise comparisons of the questionnaire with a significance level < 0.008. For other analyses, a p-value below 0.05 was considered statistically significant. Multivariable linear models of chronic fatigue symptoms included all variables that showed an association with the number of symptoms in the univariable model ($p < 0.10$) and did not substantially correlate with other independent variables ($r > 0.5$). All of the models were adjusted for age and sex. Independent predictors were obtained with the stepwise backward procedure, R was calculated, and models were checked with the F test. Data was analysed using STATISTICA 13.0 software (Statsoft Inc, Tulsa, OK, USA).

Results

The dataset confirming the results of this study may be obtained from the corresponding author upon reasonable request.

Patient characteristics

A total of 204 patients (40.2% women, median age 58 years) hospitalised due to COVID-19 were enrolled in our study. The median observation time was 187 (156–220) days from the first positive nasal swab test for SARS-CoV-2. At least one comorbidity was found in 84.31% (n = 172) of patients, and 34.41% (n = 70) had > 3 chronic diseases, the most common being hypertension, obesity, smoking, and hypercholesterolemia (Tab. 1). The prevalence of chronic

Table 1. Demographics and characteristics of patients on hospital admission

Demographics	All patients (n = 204)
Age (years)	58 (46–66)
Female sex, n (%)	82 (40.20)
Comorbidities	
Hypertension, n (%)	91 (44.61)
Hypercholesterolemia, n (%)	43 (21.08)
Obesity, n (%)	74 (36.27)
Smoking, n (%)	58 (28.43)
Diabetes mellitus, n (%)	33 (16.18)
Ischaemic heart disease, n (%)	21 (10.29)
Atrial fibrillation, n (%)	13 (6.34)
Chronic heart failure	8 (3.92)
Prior CNS disease, n (%)	
Stroke in past	10 (4.90)
Dementia	14 (6.86)
Depression	23 (11.27)
Anxiety disorders	10 (4.90)
Asthma/COPD, n (%)	21 (10.29)
Neoplasm, n (%)	
— active	4 (1.96)
— in past	12 (5.88)
Chronic kidney disease stage III, n (%)	8 (3.92)
Alcohol abuse, n (%)	5 (2.45)
Treatment	
Anticoagulant, n (%)	16 (7.84)
Beta-adrenolytic, n (%)	38 (18.63)
Antidepressant, n (%)	25 (12.25)
Neuroleptic, n (%)	6 (2.94)
Benzodiazepine, n (%)	4 (1.96)
First COVID-19 symptoms	
Anosmia n (%)	40 (19.61)
Cough, n (%)	172 (84.31)
Dyspnoea, n (%)	138 (67.65)
Fever, n (%)	174 (85.29)
Gastrointestinal, n (%)	68 (33.33)
Hospital admission	
Oxygen therapy, n (%)	
Not required	26 (12.75)
Nasal cannula	137 (67.16)
Simple face mask	40 (19.61)
Non-invasive ventilation	1 (0.49)
MEWS score, n (%)	
1	157 (76.97)
2	33 (16.18)
3	14 (6.86)
Laboratory parameters	
CRP (mg/dL) (first 24 hours)	69.3 (31.7–110.0)
IL-6 (pg/mL) (first 48 hours)	33.3 (13.1–56.2)
Procalcitonin (ng/mL) (first 24 hours)	0.09 (0.05–0.17)
WBC ($\times 10^3$) (first 24 hours)	5.61 (4.10–7.50)

Values are presented as numbers and percentages [n, (%)] and median (interquartile range).
COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein; CNS — central nervous system; IL-6 — interleukin-6; MEWS — Modified Early Warning Score; WBC — white blood cell count

Table 2. Prevalence of chronic fatigue symptoms prior to COVID-19 and within different time intervals since onset of infection

	Prior to COVID-19	0–4 weeks (acute phase)		4–12 weeks (post-acute phase)		> 12 weeks (chronic phase)	
	n (%)	n (%)	p-value *vs.* baseline	n (%)	p-value *vs.* baseline	n (%)	p-value *vs.* baseline
1.1 Persistent fatigue, not caused by effort, persisting after rest	31 (15.20)	123 (60.29)	< 0.001	111 (54.41)	< 0.001	86 (42.16)	< 0.001
1.2 Sore throat	10 (4.90)	39 (19.12)	< 0.001	26 (12.75)	0.001	26 (12.75)	< 0.001
1.3 Self-reported lymph node enlargement	2 (0.98)	16 (7.84)	< 0.001	8 (3.92)	0.034	9 (4.41)	0.020
1.4 Myalgia	31 (15.20)	101 (49.51)	< 0.001	79 (38.73)	< 0.001	62 (30.39)	< 0.001
1.5 Arthralgia	12 (5.88)	31 (15.20)	< 0.001	29 (14.21)	< 0.001	31 (15.19)	< 0.001
1.6 Headache	28 (13.72)	79 (38.73)	< 0.001	61 (29.90)	< 0.001	45 (22.06)	0.004
1.7 Non-restorative sleep	41 (20.10)	97 (47.55)	< 0.001	89 (43.63)	< 0.001	74 (36.28)	< 0.001
1.8 Prolonged post-exercise fatigue	41 (20.10)	128 (62.75)	< 0.001	118 (57.84)	< 0.001	99 (48.52)	< 0.001

Data is presented as numbers (n) and percentages (%) and compared with Cochran Q test for dependent variable. Bonferroni correction was applied for multiple pairwise comparisons, and significance level was < 0.008

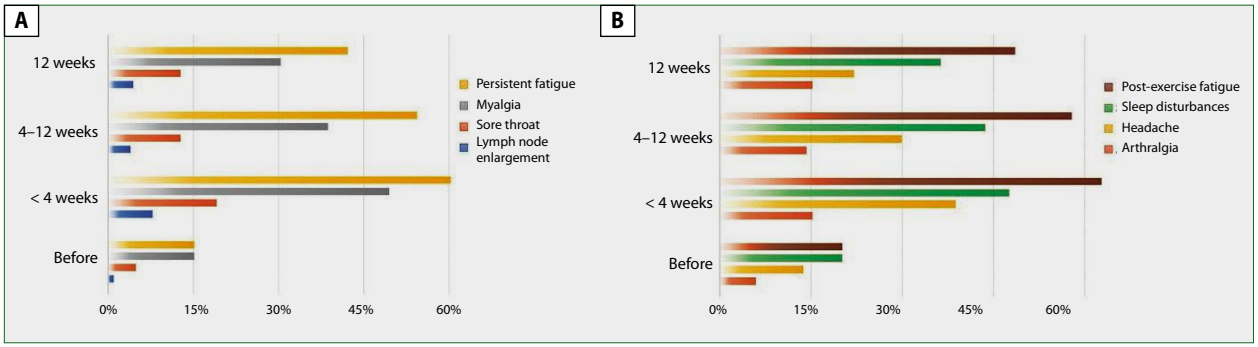

Figure 1. Pattern of chronic fatigue symptoms in acute (< 4 weeks), subacute (4–12 weeks), and chronic (> 12 weeks) phases of SARS-CoV-2 infection

heart failure, stroke, stage III chronic kidney disease, and active neoplasm was below 5%. Almost one in seven patients (14.71%, n = 30) had depression or anxiety disorders, and 16.17% (n = 33) were being treated with antidepressants, benzodiazepines, and neuroleptics.

The first symptoms of COVID-19 that were the most frequent were fever, cough and dyspnoea. On admission, laboratory tests showed a marked increase in C-reactive protein (CRP) and interleukin-6 (IL-6). During hospitalisation, 5.88% (n = 12) of patients were admitted to the Intensive Care Unit, 87.25% (n = 178) required oxygen therapy, mainly with a nasal cannula or simple oxygen mask, and none were mechanically ventilated (Tab. 1).

Chronic fatigue symptoms before and after COVID-19

Before COVID-19, 43.62% (n = 89) of patients reported at least one symptom of chronic fatigue (Tab. 2, Fig. 1). Within 4, 4–12, and > 12 weeks after COVID-19, the prevalence of chronic fatigue increased to 76.96% (n = 157), 75.49% (n = 154), and 66.17% (n = 135) of patients, respectively (all $p < 0.001$). The mean (± standard deviation) number of symptoms was 0.96 ± 1.41 prior to the SARS-CoV-2 infection, but increased to 3.01 ± 2.31, 2.55 ± 2.07 and 2.11 ± 2.04 for 4, 4–12, and > 12 weeks post-COVID, respectively ($p < 0.05$ with post-hoc Friedman ANOVA).

Table 3. Predictors of numerous symptoms of post-COVID-19 chronic fatigue in acute (< 4 weeks), subacute (4–12 weeks), and chronic (> 12 weeks) phases of infection, assessed retrospectively

< 4 weeks after onset of COVID-19	Univariable analysis		Multivariable analysis	
	β (95% CI)	p-value	β (95% CI)	p-value
Age (per year)	–0.12 (–0.25; 0.02)	0.097	–0.12 (–0.28; –0.01)	0.029
Female sex	0.23 (0.10; 0.37)	< 0.001	0.25 (0.12; 0.39)	< 0.001
Neoplasm in past	–0.11 (–0.26; 0.02)	0.091	–	–
Stroke in past	0.08 (–0.06; 0.21)	0.268	–	–
			R = 0.30, F = 6.56	
4–12 weeks after onset of COVID-19				
Age (per year)	–	0.745	–	–
Female sex	0.24 (0.07; 0.37)	< 0.001	0.25 (0.12; 0.39)	< 0.001
Antidepressants	0.12 (–0.01; 0.26)	0.077	–	–
MEWS score > 1	–0.11 (–0.25; 0.02)	0.092	–	–
			R = 0.24, F = 12.34	
> 12 weeks after onset of COVID-19				
Age (per year)	–	0.526	–	–
Female sex	0.26 (0.13; 0.40)	< 0.001	0.26 (0.13; 0.39)	< 0.001
Asthma/COPD	0.12 (–0.01; 0.26)	0.072	–	–
MEWS score > 1	–	0.275	–	–
			R = 0.26, F = 14.78	

In the first four weeks after infection, more than half of patients reported persistent fatigue not caused by effort, and post-exercise fatigue. The least frequent symptoms were lymph node enlargement, arthralgia, and sore throat (all < 20%). The frequency of symptoms decreased over the following weeks, but did not return to baseline values, except for self-reported lymph node enlargement. Furthermore, four out of 10 convalescents reported persistent fatigue not caused by effort, as well as post-exercise fatigue.

Determinants of chronic fatigue

Patients in the highest quartile of chronic fatigue symptoms were more frequently women compared to the first quartile (Suppl. Tab. 1). Interestingly, we did not observe an association between symptoms of chronic fatigue and numerous variables such as demographics, comorbidities, the first symptoms of COVID-19, severity score at admission, oxygen therapy, or pharmacological treatment, except for the higher prevalence of stroke in the past for analysis in the 4-week interval. In the multivariable linear regression model, the number of fatigue symptoms was predicted by female sex (all intervals) and age (< 4 weeks) (Tab. 3).

Discussion

Our study revealed that female sex was the only independent predictor of fatigue in a cohort of previously hospitalised patients, both in the acute phase of COVID-19 and also four and 12 weeks since the onset of infection. Our results accord with a recent Italian study of 247 patients that also confirmed the prognostic role of female sex in the persistence of neurological and psychiatric symptoms, including fatigue, seven weeks after the initial SARS-CoV-2 infection [31]. However, researchers also pointed to older age and the presence of comorbidities, especially depression, as additional risk factors for residual post-COVID symptoms, but that cohort comprised individuals approximately one decade younger than ours, with only less than half of them requiring hospitalisation due to COVID-19 [31]. Another recent study revealed that among 400 Brazilian patients previously hospitalised due to COVID-19, female sex, hypercholesterolemia, obesity and prone position in the acute phase of disease increased the risk of post-COVID syndrome, with fatigue prevalent in 42% and 27% of cases within three and six months after discharge, respectively [32]. These patients were at similar median age as in our study, but were more affected by comorbid conditions including hypertension and diabetes mellitus [32]. Another study of 504 previously hospitalised patients from Saudi Arabia followed-up three months after the onset of infection showed that the presence of post-COVID syndrome, with fatigue constituting its most common presentation, was associated with female sex, three or more comorbidities, steroid treatment, and symptoms of nasal congestion and depression during the acute phase of disease [33]. Female predominance among subjects with persistent post-COVID symptoms, with the most common being fatigue, sleep disturbances, and myalgia, was also confirmed in a cohort of 312 patients with cancer observed up to 14 months post-infection [34]. In a large cohort of more

than 12,000 adult patients from Sweden who were hospitalised due to COVID-19, it was found that post-COVID symptoms, with the prevalence of fatigue being 22%, were more common in women of middle age, and association with asthma and mental health disorders was less prominent compared to non-hospitalised individuals [35]. Interestingly, data from German health insurance organisations showed that CFS was more common in adults with COVID-19 than in the control group, whereas in children and adolescents there were no statistically significant differences between those infected with SARS-CoV-2 and unaffected individuals [36].

On the other hand, among more than 600 children and adolescents previously hospitalised due to COVID-19 in Argentina, risk factors for long COVID, with headache, cough, and fatigue comprising the most common symptoms, included older age apart from symptomatic infection and comorbidities, including diabetes [37]. In an Italian cohort of 428 patients, assessed 4–12 weeks after hospital discharge, it was found that female sex and severe SARS-CoV-2 infection were the main risk factors for post-COVID manifestations, among which chronic dyspnoea and fatigue were the most common [38]. Finally, a recent Czech study examining healthcare workers at least 12 weeks after the onset of SARS-CoV-2 infection, revealed that female sex and increasing age were the only significant predictors of post-COVID syndrome, with almost half of those patients reporting fatigue interfering with their daily life [39].

Therefore, it seems that female sex is the only consistent risk factor for residual post-COVID fatigue, both in younger [40] and older populations [41]. Notably, our cohort consisted mainly of patients in a relatively good clinical condition prior to the SARS-CoV-2 infection, as the prevalence of diseases known to increase COVID-associated mortality, such as stroke, dementia and neoplasm, was below 10% [3, 42–44].

Our study also showed that, despite a tendency to improve most patients still suffered from symptoms of fatigue within 12 weeks since the onset of the SARS-CoV-2 infection. Our results were similar to the conclusions coming from a longitudinal observation of nearly 2,000 Spanish patients, where fatigue only slightly improved between 8.4 and 13.2 months after hospital discharge, with more than half of individuals reporting this residual symptom [45]. Slow recovery from fatigue was also observed in a Danish post-COVID clinic where among 447 previously generally healthy individuals, of whom only 12% needed hospitalisation, as many as 33% and 62% of them reported moderate and severe fatigue, respectively, within six months of the onset of infection [46]. An observation of more than 9,000 Dutch patients, most of whom did not require hospitalisation, showed that three months after the SARS-CoV-2 infection, fatigue was significantly more often reported compared to the control group, with nearly half of the patients suffering from at least one residual post-COVID symptom. Interestingly, previous vaccination was not protective against fatigue, muscle and joint pain at three months [47].

On the other hand, in a group of 1,638 COVID-19 survivors, Egyptian researchers found that those fully vaccinated against SARS-CoV-2 exhibited significantly less severe post-COVID fatigue, and the presence of residual symptoms after SARS-CoV-2 infection was predicted only by its initial severity and a lack of previous vaccination [48]. A recent review of 33 studies revealed that the most common persistent post-COVID symptoms included not only chronic fatigue but also other elements of the CFS such as arthralgia, myalgia and intolerance to exertion [49]. Similarly, another systematic review of 24 articles showed that long COVID patients very commonly not only suffered from fatigue, but also reported myalgia and arthralgia [50]. Moreover, a prospective multicentre study in non-hospitalised subjects with COVID-19 showed that, despite improvement, patients still reported the persistence not only of fatigue but also of myalgia and headache within 12 weeks since the onset of infection [51]. Additionally, an international survey in a group of nearly 14,000 patients from 16 countries revealed that, apart from fatigue, insomnia and excessive daytime sleepiness, also perceived as important elements of the CFS, were the most commonly reported symptoms after hospitalisation due to COVID-19 [52]. A prospective Silesian registry of 200 COVID-19 patients, assessed c.100 days since the onset of infection, revealed that most individuals, both outpatients and hospitalised, suffered from insomnia [53]. Another review including 194 studies with around 735,000 participants showed that 45% of COVID-19 survivors experienced at least one post-COVID symptom, regardless of hospitalisation status, with the most common being fatigue [54]. However, a recent tele-assessment of COVID-19 survivors 1-6 months after their positive RT-PCR test showed that their score in a 30-second Chair Stand Test, used previously to assess fatigue effect [55], was significantly higher in outpatients compared to those requiring hospitalisation [56].

Thus, our study confirmed that a substantial proportion of patients still suffered from the symptoms of CFS within three months since the onset of SARS-CoV-2 infection.

Currently, many pathophysiological explanations for post-COVID fatigue are merely hypothesised. It has been postulated for example that SARS-CoV-2 infection may act as a trigger activating a complex network of neuropsychiatric symptoms, including fatigue, anxiety, depression, sleep and cognitive disturbances [57]. Fatigue, apart from anxiety and depression, could, in turn, significantly affect cognitive abilities even months after the initial infection [58, 59]. It has also been found that individuals with post-COVID symptoms assessed six months after hospital discharge expressed higher levels of interleukin-8 (IL-8), vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein-1 (MCP-1) compared to people without post-COVID sequelae [60, 61]. Lately, changes in retinal microcirculation visualised using optical coherence tomography angiography have been shown to be a possible marker for chronic fatigue in patients after

COVID-19 [62], and high anti-SARS-CoV-2 immunoglobulin E levels have been found to correlate with a deterioration of physical function in patients after the acute phase of SARS-CoV-2 infection [63].

It has also been suggested that post-COVID fatigue syndrome might be due to damage to the sensory olfactory neurons leading to a reduction in cerebrospinal fluid flow through the cribriform plate and, consequently, reduced removal of brain waste [64]. Inflammation associated with COVID-19 [65–67] may also impair GABAergic transmission within the brain [68], as was shown during neurophysiological studies in a small cohort of 12 patients who recovered from the SARS-CoV-2 infection [69]. Disruption of transforming growth factor beta signalling, similar to that observed in myalgic encephalomyelitis/CFS, has also been proposed, and this is something which influences circadian rhythm [70]. Incomplete recovery of the immune system, together with initial lung or liver damage, and coagulation disturbances, have also been suggested in the pathophysiology of long COVID [71]. Interestingly, a recent review of 108 patients in the post-COVID ambulatory at the Mayo Clinic in the US showed that women more often exhibited the post-COVID phenotype with predominant fatigue, while dyspnoea was the leading clinical feature in men [72]. The authors were able to show that sex-related differences in the post-COVID phenotype could be attributed to various pathophysiology as the prevalence of fatigue was associated with an elevation of IL-6 levels that was more common than an increase in CRP or erythrocyte sedimentation rate [72].

This observation could at least partially explain the prognostic role of sex in post-COVID fatigue, as has been shown in previous studies, and confirmed in our research.

Our study has important limitations. Firstly, the study sample was rather small and consisted of individuals with a relatively good pre-COVID clinical status. However, we gathered detailed data regarding demographics, comorbidities, treatment, and laboratory tests. Secondly, the results were based on responses given retrospectively by patients a few months after the initial SARS-CoV-2 infection, which could have resulted in potential bias or underestimation of symptoms. Nevertheless, most patients reported residual fatigue, which aligned with findings from previous studies [73]. Thirdly, the NP-COVID questionnaire was created for the purposes of this study; however, it was validated as described before [24]. Fourthly, our study focused on patients with wild-type or Alpha variant SARS-CoV-2; therefore, the presented results might not be applicable to other variants, especially given that individuals infected with Omicron have been shown to be less likely to exhibit long-COVID [74]. Fifthly, we did not collect data on neuroimaging, both in the acute and chronic phase of the SARS-CoV-2 infection; however, its role in evaluating fatigue may become increasingly important, as has been recently shown for conditions other than COVID-19 [75].

In conclusion, most patients previously hospitalised due to COVID-19 suffer from fatigue symptoms within 12 weeks after the onset of the infection. The presence of fatigue is predicted by female sex and — though only for the acute phase — by age. Future studies on larger patient populations are needed to seek other potential risk factors for post-COVID fatigue and — hopefully — to deliver treatment options [76, 77].

Conflict of interest: *None.*
Funding: *None.*

References

1. Garg A, Subramain M, Barlow PB, et al. Patient experiences with a tertiary care post-COVID-19 clinic. J Patient Exp. 2023; 10: 23743735231151539, doi: 10.1177/23743735231151539, indexed in Pubmed: 36698619.
2. González-Herazo MA, Silva-Muñoz DC, Guevara-Martínez PA, et al. Post-COVID 19 Neurological Syndrome: a fresh challenge in neurological management. Neurol Neurochir Pol. 2021; 55(4): 413–414, doi: 10.5603/PJNNS.a2021.0052, indexed in Pubmed: 34346051.
3. Wnuk M, Sawczyńska K, Kęsek T, et al. Neurological symptoms in hospitalised patients with COVID-19 and their association with in-hospital mortality. Neurol Neurochir Pol. 2021; 55(3): 314–321, doi: 10.5603/PJNNS.a2021.0039, indexed in Pubmed: 34037979.
4. Chudzik M, Lewek J, Kapusta J, et al. Predictors of long COVID in patients without comorbidities: data from the polish long-covid cardiovascular (polocov-cvd) study. J Clin Med. 2022; 11(17), doi: 10.3390/jcm11174980, indexed in Pubmed: 36078910.
5. Romero-Rodríguez E, Perula-de-Torres LÁ, González-Lama J, et al. Long COVID symptomatology and associated factors in primary care patients: the EPICOVID-AP21 study. Healthcare (Basel). 2023; 11(2), doi: 10.3390/healthcare11020218, indexed in Pubmed: 36673587.
6. Baskett WI, Qureshi AI, Shyu D, et al. COVID-specific long-term sequelae in comparison to common viral respiratory infections: an analysis of 17 487 infected adult patients. Open Forum Infect Dis. 2023; 10(1): ofac683, doi: 10.1093/ofid/ofac683, indexed in Pubmed: 36686632.
7. Gorelik Y, Dror A, Zayyad H, et al. Associations between reported post-COVID-19 symptoms and subjective well-being, Israel, July 2021 - April 2022. Epidemiol Infect. 2023; 151: e16, doi: 10.1017/S0950268822001996, indexed in Pubmed: 36698161.
8. Shanbehzadeh S, Zanjari N, Yassin M, et al. Association between long COVID, functional activity, and health-related quality of life in older adults. BMC Geriatr. 2023; 23(1): 40, doi: 10.1186/s12877-023-03757-w, indexed in Pubmed: 36690948.
9. Nielsen TB, Leth S, Pedersen M, et al. Mental fatigue, activities of daily living, sick leave and functional status among patients with long COVID: a cross-sectional study. Int J Environ Res Public Health. 2022; 19(22), doi: 10.3390/ijerph192214739, indexed in Pubmed: 36429458.
10. Chatys-Bogacka Z, Mazurkiewicz I, Slowik J, et al. Brain fog and quality of life at work in non-hospitalized patients after COVID-19. Int J Environ Res Public Health. 2022; 19(19), doi: 10.3390/ijerph191912816, indexed in Pubmed: 36232113.
11. Walter N, Rupp M, Lang S, et al. A comprehensive report of German nationwide inpatient data on the post-covid-19 syndrome including

annual direct healthcare costs. Viruses. 2022; 14(12), doi: 10.3390/v14122600, indexed in Pubmed: 36560604.
12. Pillay J, Rahman S, Guitard S, et al. Risk factors and preventive interventions for post Covid-19 condition: systematic review. Emerg Microbes Infect. 2022; 11(1): 2762–2780, doi: 10.1080/22221751.2022.2140612, indexed in Pubmed: 36302216.
13. Alkwai HM, Khalifa AM, Ahmed AM, et al. Persistence of COVID-19 symptoms beyond 3 months and the delayed return to the usual state of health in Saudi Arabia: A cross-sectional study. SAGE Open Med. 2022; 10: 20503121221129918, doi: 10.1177/20503121221129918, indexed in Pubmed: 36226231.
14. Arjun MC, Singh AK, Pal D, et al. Characteristics and predictors of Long COVID among diagnosed cases of COVID-19. PLoS One. 2022; 17(12): e0278825, doi: 10.1371/journal.pone.0278825, indexed in Pubmed: 36538532.
15. Fernández-de-Las-Peñas C, Rodríguez-Jiménez J, Cancela-Cilleruelo I, et al. Post-COVID-19 symptoms 2 years after SARS-CoV-2 infection among hospitalized vs nonhospitalized patients. JAMA Netw Open. 2022; 5(11): e2242106, doi: 10.1001/jamanetworkopen.2022.42106, indexed in Pubmed: 36378309.
16. Domènech-Montoliu S, Puig-Barberà J, Pac-Sa MR, et al. Complications Post-COVID-19 and Risk Factors among Patients after Six Months of a SARS-CoV-2 Infection: A Population-Based Prospective Cohort Study. Epidemiologia (Basel). 2022; 3(1): 49–67, doi: 10.3390/epidemiologia3010006, indexed in Pubmed: 36417267.
17. Kubota T, Kuroda N, Sone D. Neuropsychiatric aspects of long COVID: a comprehensive review. Psychiatry Clin Neurosci. 2023; 77(2): 84–93, doi: 10.1111/pcn.13508, indexed in Pubmed: 36385449.
18. Važgėlienė D, Kubilius R, Bileviciute-Ljungar I. Do comorbidities and daily medication before SARS-CoV-2 infection play a role in self-reported post-infection symptoms? J Clin Med. 2022; 11(21), doi: 10.3390/jcm11216278, indexed in Pubmed: 36362506.
19. Patel UK, Mehta N, Patel A, et al. Long-term neurological sequelae among severe COVID-19 patients: a systematic review and meta-analysis. Cureus. 2022; 14(9): e29694, doi: 10.7759/cureus.29694, indexed in Pubmed: 36321004.
20. Nakano Y, Otsuka Y, Honda H, et al. Transitional changes in fatigue-related symptoms due to long COVID: a single-center retrospective observational study in japan. Medicina (Kaunas). 2022; 58(10), doi: 10.3390/medicina58101393, indexed in Pubmed: 36295554.
21. Bernas SN, Baldauf H, Real R, et al. Post-COVID-19 condition in the German working population: a cross-sectional study of 200,000 registered stem cell donors. J Intern Med. 2023; 293(3): 354–370, doi: 10.1111/joim.13587, indexed in Pubmed: 36373223.
22. Stavem K, Ghanima W, Olsen MK, et al. Prevalence and determinants of fatigue after COVID-19 in non-hospitalized subjects: a population-based study. Int J Environ Res Public Health. 2021; 18(4), doi: 10.3390/ijerph18042030, indexed in Pubmed: 33669714.
23. Kim Y, Kim SW, Chang HH, et al. Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea. BMC Infect Dis. 2022; 22(1): 93, doi: 10.1186/s12879-022-07062-6, indexed in Pubmed: 35086489.
24. Mazurkiewicz I, Chatys-Bogacka Z, Slowik J, et al. Fatigue after COVID-19 in non-hospitalized patients according to sex. Brain and Behavior. 2023; 13(2), doi: 10.1002/brb3.2849.
25. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994; 121(12): 953–959, doi: 10.7326/0003-4819-121-12-199412150-00009, indexed in Pubmed: 7978722.
26. Lim EJ, Son CG. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J Transl Med. 2020; 18(1): 289, doi: 10.1186/s12967-020-02455-0, indexed in Pubmed: 32727489.
27. Azcue N, Gómez-Esteban JC, Acera M, et al. Brain fog of post-COVID-19 condition and Chronic Fatigue Syndrome, same medical disorder? J Transl Med. 2022; 20(1): 569, doi: 10.1186/s12967-022-03764-2, indexed in Pubmed: 36474290.
28. Sukocheva OA, Maksoud R, Beeraka NM, et al. Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. J Adv Res. 2022; 40: 179–196, doi: 10.1016/j.jare.2021.11.013, indexed in Pubmed: 36100326.
29. COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE, London 2020.
30. Shah W, Hillman T, Playford ED, et al. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ. 2021; 372: n136, doi: 10.1136/bmj.n136, indexed in Pubmed: 33483331.
31. Sansone D, Tassinari A, Valentinotti R, et al. Persistence of symptoms 15 months since COVID-19 diagnosis: prevalence, risk factors and residual work ability. Life (Basel). 2022; 13(1), doi: 10.3390/life13010097, indexed in Pubmed: 36676046.
32. Lapa J, Rosa D, Mendes JP, et al. Prevalence and associated factors of post-COVID-19 syndrome in a Brazilian cohort after 3 and 6 months of hospital discharge. Int J Environ Res Public Health. 2023; 20(1), doi: 10.3390/ijerph20010848, indexed in Pubmed: 36613170.
33. Alghamdi SA, Alfares MA, Alsulami RA, et al. Post-COVID-19 syndrome: incidence, risk factor, and the most common persisting symptoms. Cureus. 2022; 14(11): e32058, doi: 10.7759/cureus.32058, indexed in Pubmed: 36600841.
34. Dagher H, Chaftari AM, Subbiah IM, et al. Long COVID in cancer patients: preponderance of symptoms in majority of patients over long time period. Elife. 2023 [Epub ahead of print]; 12, doi: 10.7554/eLife.81182, indexed in Pubmed: 36748905.
35. Hedberg P, Granath F, Bruchfeld J, et al. Post COVID-19 condition diagnosis: a population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection. J Intern Med. 2023; 293(2): 246–258, doi: 10.1111/joim.13584, indexed in Pubmed: 36478477.
36. Roessler M, Tesch F, Batram M, et al. Post-COVID-19-associated morbidity in children, adolescents, and adults: a matched cohort study including more than 157,000 individuals with COVID-19 in Germany. PLoS Med. 2022; 19(11): e1004122, doi: 10.1371/journal.pmed.1004122, indexed in Pubmed: 36355754.
37. Seery V, Raiden S, Penedo JM, et al. Persistent symptoms after COVID-19 in children and adolescents from Argentina. Int J Infect Dis. 2023 [Epub ahead of print], doi: 10.1016/j.ijid.2023.01.031, indexed in Pubmed: 36736574.
38. Spinicci M, Graziani L, Tilli M, et al. Infection with SARS-CoV-2 variants is associated with different long COVID phenotypes. Viruses. 2022; 14(11), doi: 10.3390/v14112367, indexed in Pubmed: 36366465.
39. Štěpánek L, Nakládalová M, Janošíková M, et al. Predictors and characteristics of post-acute COVID-19 syndrome in healthcare workers. Infect Dis (Lond). 2023; 55(2): 125–131, doi: 10.1080/23744235.2022.2136750, indexed in Pubmed: 36285402.
40. Buonsenso A, Murri A, Centorbi M, et al. Psychological wellbeing and perceived fatigue in competitive athletes after SARS-CoV-2 infection 2 years after pandemic start: practical indications. J Funct Morphol Kinesiol. 2022; 8(1), doi: 10.3390/jfmk8010001, indexed in Pubmed: 36648893.

41. Daitch V, Yelin D, Awwad M, et al. ESCMID study group for infections in the elderly (ESGIE). Characteristics of long-COVID among older adults: a cross-sectional study. Int J Infect Dis. 2022; 125: 287–293, doi: 10.1016/j.ijid.2022.09.035, indexed in Pubmed: 36191820.
42. Zielińska-Turek J, Jasińska A, Kołakowska J, et al. Clinical features of neurological patients with coronavirus 2019: an observational study of one centre. Neurol Neurochir Pol. 2021; 55(2): 195–201, doi: 10.5603/PJNNS.a2021.0011, indexed in Pubmed: 33528832.
43. Drabik L, Derbisz J, Chatys-Bogacka Z, et al. Neurological prognostic factors in hospitalized patients with COVID-19. Brain Sci. 2022; 12(2), doi: 10.3390/brainsci12020193, indexed in Pubmed: 35203956.
44. Sawczyńska K, Wnuk M, Jagiełła J, et al. 4C Mortality Score correlates with in-hospital functional outcome after COVID-19-associated ischaemic stroke. Neurol Neurochir Pol. 2021; 55(3): 295–299, doi: 10.5603/PJNNS.a2021.0037, indexed in Pubmed: 33949676.
45. Fernández-de-Las-Peñas C, Martín-Guerrero JD, Cancela-Cilleruelo I, et al. Exploring the recovery curve for long-term post-COVID dyspnea and fatigue. Eur J Intern Med. 2022; 101: 120–123, doi: 10.1016/j.ejim.2022.03.036, indexed in Pubmed: 35490087.
46. Agergaard J, Ullahammer WM, Gunst JD, et al. Characteristics of a danish post-COVID cohort referred for examination due to persistent symptoms six months after mild acute COVID-19. J Clin Med. 2022; 11(24), doi: 10.3390/jcm11247338, indexed in Pubmed: 36555954.
47. van der Maaden T, Mutubuki EN, de Bruijn S, et al. Prevalence and severity of symptoms 3 months after infection with SARS-CoV-2 compared to test-negative and population controls in the Netherlands. 2022, doi: 10.1101/2022.06.15.22276439.
48. Elmazny A, Magdy R, Hussein M, et al. Neuropsychiatric post-acute sequelae of COVID-19: prevalence, severity, and impact of vaccination. Eur Arch Psychiatry Clin Neurosci. 2023 [Epub ahead of print]: 1–10, doi: 10.1007/s00406-023-01557-2, indexed in Pubmed: 36707454.
49. Surapaneni KM, Singhal M, Saggu SR, et al. A scoping review on long COVID-19: physiological and psychological symptoms post-acute, long-post and persistent post COVID-19. Healthcare (Basel). 2022; 10(12), doi: 10.3390/healthcare10122418, indexed in Pubmed: 36553942.
50. Swarnakar R, Jenifa S, Wadhwa S. Musculoskeletal complications in long COVID-19: a systematic review. World J Virol. 2022; 11(6): 485–495, doi: 10.5501/wjv.v11.i6.485, indexed in Pubmed: 36483107.
51. Hedin K, van der Velden AW, Hansen MP, et al. Initial symptoms and three months follow-up after acute COVID-19 in outpatients: An international prospective cohort study. Eur J Gen Pract. 2023 [Epub ahead of print]: 2154074, doi: 10.1080/13814788.2022.2154074, indexed in Pubmed: 36655704.
52. Merikanto I, Dauvilliers Y, Chung F, et al. Sleep symptoms are essential features of long-COVID - Comparing healthy controls with COVID-19 cases of different severity in the international COVID sleep study (ICOSS-II). J Sleep Res. 2023; 32(1): e13754, doi: 10.1111/jsr.13754, indexed in Pubmed: 36208038.
53. Niedziela JT, Głowacki J, Ochman M, et al. Post-COVID19 complications in hospitalized and nonhospitalized patients: the Silesian database of COVID19 complications (SILCOV19). Pol Arch Intern Med. 2022; 132(6), doi: 10.20452/pamw.16233, indexed in Pubmed: 35292614.
54. O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. EClinicalMedicine. 2023; 55: 101762, doi: 10.1016/j.eclinm.2022.101762, indexed in Pubmed: 36474804.
55. Millor N, Lecumberri P, Gómez M, et al. An evaluation of the 30-s chair stand test in older adults: frailty detection based on kinematic parameters from a single inertial unit. J Neuroeng Rehabil. 2013; 10: 86, doi: 10.1186/1743-0003-10-86, indexed in Pubmed: 24059755.
56. Yilmaz Gokmen G, Durmaz D, Demir C, et al. Determining post-COVID-19 symptoms and rehabilitation needs in hospitalized and nonhospitalized COVID-19 survivors with tele-assessment methods. Telemed J E Health. 2023 [Epub ahead of print], doi: 10.1089/tmj.2022.0349, indexed in Pubmed: 36757300.
57. Scharfenberg D, Schild AK, Warnke C, et al. A network perspective on neuropsychiatric and cognitive symptoms of the post-COVID syndrome. Eur J Psychol. 2022; 18(4): 350–356, doi: 10.5964/ejop.10097, indexed in Pubmed: 36605094.
58. Cavaco S, Sousa G, Gonçalves A, et al. Predictors of cognitive dysfunction one-year post COVID-19. Neuropsychology. 2023 [Epub ahead of print], doi: 10.1037/neu0000876, indexed in Pubmed: 36603126.
59. Burton C, Dawes H, Goodwill S, et al. Within and between-day variation and associations of symptoms in Long Covid: Intensive longitudinal study. PLoS One. 2023; 18(1): e0280343, doi: 10.1371/journal.pone.0280343, indexed in Pubmed: 36656830.
60. Alfadda AA, Rafiullah M, Alkhowaiter M, et al. Clinical and biochemical characteristics of people experiencing post-coronavirus disease 2019-related symptoms: A prospective follow-up investigation. Front Med (Lausanne). 2022; 9: 1067082, doi: 10.3389/fmed.2022.1067082, indexed in Pubmed: 36561720.
61. Płazak W, Drabik L. SARS-CoV-2 infection and SLE: endothelial dysfunction, atherosclerosis, and thrombosis. Clin Rheumatol. 2023 [Epub ahead of print]: 1–12, doi: 10.1007/s10067-022-06497-1, indexed in Pubmed: 36622519.
62. Schlick S, Lucio M, Wallukat G, et al. Post-COVID-19 syndrome: retinal microcirculation as a potential marker for chronic fatigue. Int J Mol Sci. 2022; 23(22), doi: 10.3390/ijms232213683, indexed in Pubmed: 36430175.
63. Giménez-Orenga K, Pierquin J, Brunel J, et al. HERV-W ENV antigenemia and correlation of increased anti-SARS-CoV-2 immunoglobulin levels with post-COVID-19 symptoms. Front Immunol. 2022; 13: 1020064, doi: 10.3389/fimmu.2022.1020064, indexed in Pubmed: 36389746.
64. Wostyn P. COVID-19 and chronic fatigue syndrome: Is the worst yet to come? Med Hypotheses. 2021; 146: 110469, doi: 10.1016/j.mehy.2020.110469, indexed in Pubmed: 33401106.
65. Bratosiewicz-Wąsik J. Neuro-COVID-19: an insidious virus in action. Neurol Neurochir Pol. 2022; 56(1): 48–60, doi: 10.5603/PJNNS.a2021.0072, indexed in Pubmed: 34642927.
66. Straburzyński M, Kuca-Warnawin E, Waliszewska-Prosół M. COVID-19-related headache and innate immune response - a narrative review. Neurol Neurochir Pol. 2022 [Epub ahead of print], doi: 10.5603/PJNNS.a2022.0049, indexed in Pubmed: 35758225.
67. Finsterer J, Scorza FA, Scorza CA. Neuro-COVID due to response against the virus. Neurol Neurochir Pol. 2022; 56(1): 103–104, doi: 10.5603/PJNNS.a2021.0089, indexed in Pubmed: 34939661.
68. Versace V, Sebastianelli L, Ferrazzoli D, et al. Intracortical GABAergic dysfunction in patients with fatigue and dysexecutive syndrome after COVID-19. Clin Neurophysiol. 2021; 132(5): 1138–1143, doi: 10.1016/j.clinph.2021.03.001, indexed in Pubmed: 33774378.
69. Ortelli P, Ferrazzoli D, Sebastianelli L, et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging

symptom. J Neurol Sci. 2021; 420: 117271, doi: 10.1016/j.jns.2020.117271, indexed in Pubmed: 33359928.
70. McCarthy MJ. Circadian rhythm disruption in myalgic encephalomyelitis/chronic fatigue syndrome: implications for the post-acute sequelae of COVID-19. Brain Behav Immun Health. 2022; 20: 100412, doi: 10.1016/j.bbih.2022.100412, indexed in Pubmed: 35465246.
71. Jiang L, An X, Duan Y, et al. The pathological mechanism of the COVID-19 convalescence and its treatment with traditional Chinese medicine. Front Pharmacol. 2022; 13: 1054312, doi: 10.3389/fphar.2022.1054312, indexed in Pubmed: 36703736.
72. Ganesh R, Grach SL, Ghosh AK, et al. The Female-Predominant Persistent Immune Dysregulation of the Post-COVID Syndrome. Mayo Clin Proc. 2022; 97(3): 454–464, doi: 10.1016/j.mayocp.2021.11.033, indexed in Pubmed: 35135695.
73. Al-Husinat L, Nusir M, Al-Gharaibeh H, et al. Post-COVID-19 syndrome symptoms after mild and moderate SARS-CoV-2 infection. Front Med (Lausanne). 2022; 9: 1017257, doi: 10.3389/fmed.2022.1017257, indexed in Pubmed: 36262270.
74. Fernández-de-Las-Peñas C, Notarte KI, Peligro PJ, et al. Long-COVID Symptoms in Individuals Infected with Different SARS-CoV-2 Variants of Concern: A Systematic Review of the Literature. Viruses. 2022; 14(12), doi: 10.3390/v14122629, indexed in Pubmed: 36560633.
75. Sobczak AM, Bohaterewicz B, Ceglarek A, et al. Brain under fatigue — can perceived fatigability in multiple sclerosis be seen on the level of functional brain network architecture? Front Hum Neurosci. 2022; 16: 852981, doi: 10.3389/fnhum.2022.852981, indexed in Pubmed: 35620154.
76. Cortés Borra A. Does amantadine have a protective effect against COVID-19? Neurol Neurochir Pol. 2020; 54(3): 284–285, doi: 10.5603/PJNNS.a2020.0041, indexed in Pubmed: 32495926.
77. Müller T, Riederer P, Kuhn W. Aminoadamantanes: from treatment of Parkinson's and Alzheimer's disease to symptom amelioration of long COVID-19 syndrome? Expert Rev Clin Pharmacol. 2023; 16(2): 101–107, doi: 10.1080/17512433.2023.2176301, indexed in Pubmed: 36726198.