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Post-COVID-19 fatigue: A cross-sectional study

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Abstract

Aim: To evaluate the prevalence of post-infection fatigue (PVFS) over one year after COVID-19.

Material and methods: 165 people who had COVID-19 more than a year ago were interviewed. A Fatigue Assessment Scale was used to assess the degree of fatigue. Chemiluminescent analysis was carried out to detect antibodies to Epstein-Barr Virus (EBV) antigens. For statistical analysis Fisher's exact test and Spearman correlation were conducted.

Results: Among people with PVFS, there were 4.1 times more women than men (80.4% vs. 19.6%), people over 45 years old (76%), and people who needed hospitalization for COVID-19 (76%). The average fatigue duration was 573±18,3 days. Among individuals without PVFS, there were significantly more individuals under the age of 45 compared with the group of individuals with PVFS (40% and 24%, respectively, p=0.007) and there were significantly more individuals who did not need hospitalization compared with the group of individuals with PVFS (52% vs. 24%, p=0.005). EBV reactivation was determined in almost half of the individuals with PVFS (48%), while none of the individuals without PVFS had EBV reactivation. A statistically significant negative mean correlation was found between the duration of PVFS and the severity of PVFS (r=-0.357, p=0.007). A statistically significant negative correlation was found between the PVFS duration and the PVFS severity (r=-0.357, p=0.007).

Conclusion: PVFS is a prevalent symptom after COVID-19. The duration of PVFS can reach and not be limited to 1.5 years. PVFS is more typical of women, people over 45 years of age and people who have had moderate and severe COVID-19. Over time, the severity of PVFS decreases.

Key words: COVID-19, post-infection fatigue, Epstein-Barr virus

Introduction

The COVID-19 pandemic, which lasted almost two years and, according to WHO, affected more than 659 million people and claimed more than 6.6 million lives worldwide as of early January 2023 [1], left many unresolved issues, primarily associated with post-COVID sequels. A feature of long COVID is the presence of a wide range of symptoms of varying severity, including general symptoms such as fatigue, post-exercise malaise and fever, as well as groups of symptoms related to disorders in the functioning of various organs and systems [2-4].

There is currently no long-term evidence base to help determine how long the current effects seen after SARS-CoV-2 infection last. The term "post-covid syndrome" has been agreed to mean that the acute phase of the disease has ended, but the patient has not yet recovered.

Today, a distinction is made between prolonged fatigue (PF), chronic fatigue (CF), idiopathic chronic fatigue (ICF), and systemic exertion intolerance disease (SEID) exercise intolerance syndrome, also referred to as chronic fatigue syndrome (SCF) or myalgic encephalomyelitis (ME), which is isolated as a separate nosology. At the same time, in the spectrum of post-COVID disorders, researchers report the predominance of chronic fatigue, the signs of which developed during or immediately after COVID-19 and can be regarded as post-viral fatigue (PVFS) [5-8]. Corresponding criteria are formulated for each type of fatigue [9, 10]. To

identify fatigue, researchers usually use various questionnaires to identify feelings of mental and/or physical fatigue, as well as the fatigue effect on the respondent's quality of life [7, 11-16].

To date, researchers have shown that one of the main symptoms of long COVID is fatigue, which can be present in a patient for 6 months or more after COVID-19 [13, 17, 18]. However, the issue of the duration of this post-COVID symptom and its characteristics in a longer period has not yet been sufficiently studied.

This study is devoted to the study of the prevalence of PVFS in the period of more than one year after COVID-19.

Material and methods

The study was conducted at the Asfendiyarov Kazakh National Medical University, Kazakhstan, Almaty in October 2022.

Study design

Cross-sectional study of COVID-19 survivors over a year ago to assess long-term PVFS prevalence.

Study population

For the study, 200 individuals of both sexes with a history of PCR-confirmed COVID-19 more than one year ago were selected from the medical information system of the Ministry of Health of the Republic of Kazakhstan "Damumed", regardless of the disease severity and the fact of hospitalization during the infection acute period. A telephone call was made to these individuals, during which 165 people were interviewed. Of these, three groups were formed: individuals who indicated the post-COVID symptoms absence (n=87), individuals with PVFS (n=55) and individuals with post-COVID symptoms who did not indicate the fatigue presence (n=23). Nine individuals from the PVFS group refused to participate in the study. Thus, a study group was formed, consisting of 46 people who were examined using the Fatigue Assessment Scale (FAS) and laboratory methods. For the formation of the control group, 50 participants were randomly selected from fully recovered COVID-19 patients (Figure 1).

Inclusion Criteria

The study included people of both sexes aged 18-80 who had been ill with confirmed COVID-19 more than one year ago.

Exclusion Criteria

A history of chronic diseases: oncological, autoimmune and others, which may be manifested by fatigue and / or require treatment with cytostatics, immunosuppressive drugs, including genetically engineered biological products, as well as psychotropic drugs.

Fatigue assessment

The presence and level of fatigue was assessed using FAS. This scale was developed by Michielsen et al [19], is recommended for use and has been widely used to assess fatigue in various study cohorts since 2003 [7, 20-23]. FAS consist of 10 items. Each FAS item is scored on a five-point Likert-type scale ranging from 1 (never) to 5 (always). Items 4 and 10 are evaluated in reverse order. The score ranges from 10, indicating the lowest fatigue level, to 50, indicating the highest level of respondent fatigue.

Ethical aspects

The study was approved by the Ethics Committee of the Asfendiyarov Kazakh National Medical University (Minutes No.1 (124) of 01/26/2022).

Informed consent was obtained from all study participants after a full explanation of the purpose and methods of the study, confirmation of the confidentiality of the data obtained, and notification that they can refrain from the study at any time without explanation.

Antibodies to Epstein-Barr virus (EBV) antigens were determined by immunochemiluminescence analysis using test kits for IgM to the capsid antigen (CA), IgG and IgA to the early antigen (EA) and core antigen (NA) EBV (Maglumi, China).

The simultaneous seropositivity of IgM for EA (IGM-EA) and IgG for NA (IgG-EBNA-1) was considered a marker of EBV reactivation [24].

Statistical analysis

All statistical analyzes were performed using IBM SPSS Statistics v29.0 and statistical significance was considered p<0, 05. Descriptive statistics are presented as mean with error of mean and minimum/maximum value. We analyzed the intergroup differences between individuals with PVFS compared with those without it using Fisher's exact test. In the correlation analysis according to the data, the Spearman correlation coefficient was used.

Results

Comparative characteristics of individuals with PVFS (PVFS+) and those without it (PVFS -) are presented in Table 1.

When comparing the main characteristics in individuals with and without PVFS, a slight predominance of men in the group with no PVFS was revealed, compared with the group with PVFS (32% vs. 20%). At the same time, among individuals without PVFS, there were significantly more individuals under the age of 45 compared with the group of individuals with PVFS (40% and 24%, respectively, p=0.007). Also, significant differences were found between the compared groups in terms of the severity of COVID-19.

Table 2 Study group characteristic with PVFS (n=46)

№	Parameters		Amount, n	%
1	Sex	Male	9	20
		Female	37	80
2	Age (years)	26-44	11	24
		45-59	22	48
		60-74	9	20
		75-80 ≥	4	8
3	BMI	<18.5	1	2
		≥18.5 до < 25	22	48
		≥25	23	50
4	Required inpatient treatment for COVID-19	No	11	24
		Yes	35	76
5.	Fatigue degree*	Mild	32	70
		Moderate	9	20
		Severe	5	10
6	Average duration of fatigue at the time of the survey M±m (max/min)	573±18,3 (856/370)	-	-

* The severity of PVFS was determined according to the questionnaire:
Mild – 22-28 points
Moderate – 29-34 points
Severe – above 35 points

Table 1 Comparative characteristics of PVFS+ and PVFS – groups

Parameters		PVFS+ N=46	PVFS – N=50	P
Sex	Male	9 (20%)	16 (32%)	0,166
	Female	37 (80%)	34 (68%)	
Age (years)*	26-44	11 (24%)	20 (40%)	**0,007**
	45-59	22 (48%)	12 (24%)	
	60-74	9 (20%)	18 (36%)	
	75-80 ≥	4 (8%)	0 (0%)	
BMI**	<18.5:	1 (2%)	2 (4%)	0,770
	≥18.5 до < 25	22 (48%)	26 (52%)	
	≥25	23 (50%)	22 (44%)	
Required inpatient treatment for COVID-19	No	11 (24%)	26 (52%)	**0,005**
	Yes	35 (76%)	24 (48%)	
EBV reactivation	No	24 (52%)	50 (100%)	**<0,001**
	Yes	22 (48%)	0 (0%)	

* Age criteria were determined in accordance with WHO criteria
* BMI criteria were determined in accordance with the WHO classification

Table 3 Group's characteristic with different degrees of PVFS

Parameters	M±m	Mild (22-28 points), n=32 (100%)	Moderate (29-34 points), n=9 (100%)	Severe (above 35 points), n=5 (100%)
Sex				
Male (n=9)	28,11±1,79	5 (16%)	2 (22%)	2 (40%)
Female (n=37)	26,97±0,80	27 (84%)	7 (78%)	3 (60%)
Age				
26-44 (n=11)	27,36±1,76	8 (25%)	2 (22%)	1 (20%)
45-59 (n=22)	27±1	15 (47%)	5 (56%)	2 (40%)
60-74 (n=9)	27,44±1,60	7 (22%)	1 (11%)	1 (20%)
75-80 ≥ (n=4)	27,25±3,01	2 (6%)	1 (11%)	1 (20%)
BMI				
<18.5 (n=1)	-	0 (0%)	1 (11%)	0 (0%)
≥18.5 до < 25 (n=22)	26±1	18 (56%)	3 (33%)	1 (20%)
≥25 (n=23)	28,04±1,03	14 (44%)	5 (56%)	4 (80%)
Needed COVID-19 inpatient treatment				
No (n=36)	27,69±1,75	26 (81%)	7 (78%)	3 (60%)
Yes (n=10)	27±0,76	6 (19%)	2 (22%)	2 (40%)

Table 4 Correlation analysis results between PVFS duration, age, body mass index with PVFS severity

Parameters	Spearman's correlation coefficient	P-value
Duration of PVFS after COVID-19 (days)	-0,357	0,007
Age	0,069	0,325
BMI	0,135	0,186

Thus, in the group with no PVFS, there were significantly more individuals who did not need hospitalization compared with the group of persons with PVFS (52% vs. 24%, p=0.005).

EBV reactivation was determined in almost half of the individuals with PVFS (48%), while none of the individuals without PVFS had EBV reactivation.

The main characteristics of individuals with PVFS lasting more than 1 year after COVID-19 are presented in Table 2.

Among individuals with PVFS, there were 4.1 times more women than men (80.4% versus 19.6%). At the same time, PVFS was more common in people older than 45 years (76%). Half of those with PVFS were overweight. At the same time, 76% of individuals required hospitalization for COVID-19.

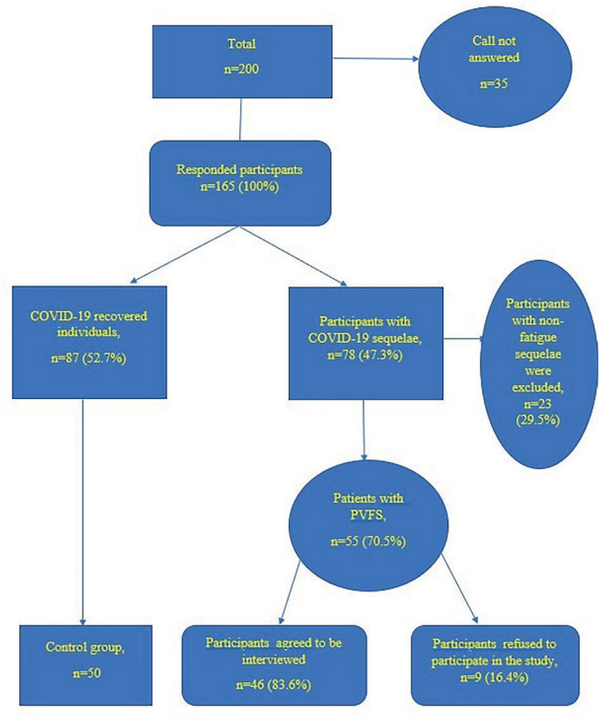

Figure 1 - Flow chart of study population

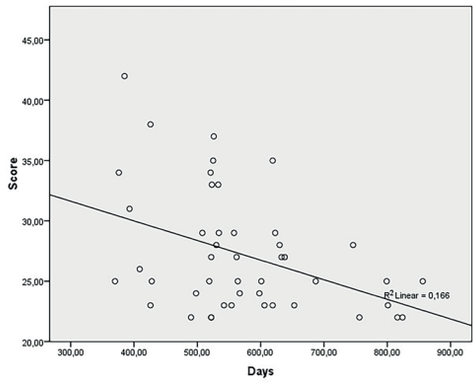

Figure 2 - Association between PVFS duration and PVFS severity

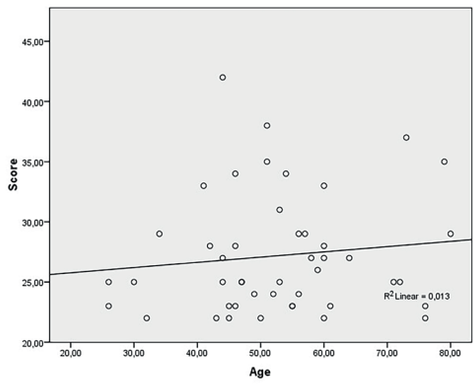

Figure 3 - Association between age and PVFS severity

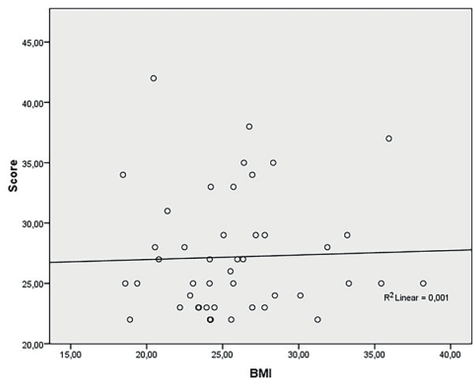

Figure 4 - Association between BMI and PVFS severity

However, 70% of individuals noted a mild degree of PVFS, while severe PVFS was observed in only 5% of individuals. The average duration of fatigue was 573 days.

Severe PVFS prevailed in women compared to men (60% versus 40%, respectively). Severe PVFS was found in 80% of overweight individuals. At the same time, a mild degree of PVFS prevailed in those who did not need hospitalization (81%) (Table 3).

The results of the correlation analysis between the duration of PVFS, age and BMI with the PVFS severity are presented in Table 4.

A statistically significant negative correlation was found between the duration of PVFS and the severity of PVFS (r=-0,357, p=0,007). A positive, non-significant weak correlation was found between age, BMI and PVFS severity (r=0,069, p=0,325 and r=0,135, p=0,186, respectively) (Figures 2-4).

Discussion

One of the main issues in the COVID-19 post-pandemic stage is how long post-COVID manifestations are and what their mechanism is.

To date, studies on the post-COVID effects duration are limited to a period of just over 1 year [25-28]. In our study, we covered a later period of 1 to 2 years. At the same time, we focused only on the PVFS manifestations, since this symptom is one of the most common sequalae of COVID-19 [29, 30], but, at the same time, due to unexpressed symptoms, it often falls out of the sight of clinicians.

In our study, it was found that in almost half of the people who had COVID-19, after 1 year, various manifestations of post-COVID complications persist, while chronic fatigue is the predominant symptom (70.5%). These data significantly exceed data on the prevalence of both idiopathic chronic fatigue (ICF) and chronic fatigue syndrome (CFS) in the adult population [31-33]. In a previously conducted pilot study of the prevalence of fatigue in the Kazakhstan population in 2018, we conducted a survey of 1000 respondents using FAS. According to this study results, pathological fatigue was found in 432 (43.2%) and no fatigue in 568 (56.8%) respondents. In the group of people with fatigue, 62.4% were women and 37.6% were men. Since we excluded individuals with comorbid conditions that may contribute to the development of chronic fatigue from the study, we can assume that this fatigue is a post-COVID consequence.

In our group of PVFS individuals, there was a predominance of women, people over 45 years old, and people who needed COVID-19 inpatient treatment, that is, people with a more severe COVID-19. Moreover, severe PVFS was observed in women 1.5 times more often than in men. These data are consistent with the results of studies by other authors in the earlier post-COVID period [25, 34].

It is assumed that the prevalence of women in the group with chronic fatigue is associated with both psychological and physiological characteristics of women, such as a lower tendency to mask symptoms, as well as neurohormonal characteristics [35].

A comparative analysis of the indicators of PVFS individuals and those without PVFS also confirmed these data, showing significant differences in age and COVID-19 severity. Interestingly, some authors noted the presence of fatigue in the earlier post-COVID period, even with mild COVID-19 [36]. At the same time, the results of our study suggest that in mild cases of COVID-19, PVFS rarely lasts more than 1 year. Even if people who recovered easily from COVID-19 noted fatigue after 1 year, this fatigue is not expressed according to our data.

The propensity to reduce the PVFS severity over time is also confirmed by the data of the correlation analysis, which revealed a significant negative relationship between the duration of PVFS and the severity of PVFS. A similar association has also been found in earlier studies [37]. We also found a weak positive relationship between age and BMI and the severity of PVFS. We believe that the lack of significant differences in our study in these parameters is due to the small sample size, which is a limitation of our study. An additional limitation is the lack of data on other potential risk factors for fatigue in the post-COVID-19 period. At the same time, the median duration of PVFS in our cohort was 573 days, suggesting that PVFS may continue for at least 1.5 years after COVID-19.

In our study, 48% of PVFS individuals had EBV reactivation. Earlier studies have shown that EBV reactivation can occur both with COVID-19 and in the post-COVID period [25, 38-41]. Since our study is cross-sectional, we cannot

identify the timing of the onset of EBV reactivation and be sure that this reactivation is associated with COVID-19. However, the prevalence of EBV reactivation in our focus group with PVFS exceeds the prevalence of EBV in risk groups associated with EBV reactivation [42, 43]. In this regard, we believe that more in-depth studies are needed to study the causes of EBV reactivation in the long-term period after COVID-19.

Conclusion

PVFS is the predominant symptom one year after COVID-19 (70.5%), which exceeds its frequency in the pre-COVID period (43.2%). The duration of PVFS has not been determined and may continue beyond 1 year after the acute phase. The average duration of PVFS was 537 days. PVFS for a period longer than 1 year persists to a greater extent in women and persons over 45 years of age. PVFS was detected in those who had COVID-19 in moderate and severe forms and received inpatient treatment. Over time, the intensity of PVFS decreases. At the same time, serological markers of EBV reactivation were detected in 48% of individuals with PVFS.

However, additional studies are needed to confirm the hypotheses put forward and to identify factors associated with the prolonged fatigue formation in the late post-COVID period.

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