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Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19

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Abstract

As the SARS-COV-2 becomes a global pandemic, many researchers have a concern about the long COVID-19 complications. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a persistent, debilitating, and unexplained fatigue disorder. We investigated psychological morbidities such as CFS and post-traumatic stress disorder (PTSD) among survivors of COVID-19 over 6 months. All COVID-19 survivors from the university-affiliated hospital of Tehran, Iran, were assessed 6 months after infection onset by a previously validated questionnaire based on the Fukuda guidelines for CFS/EM and DSM-5 Checklist for PTSD (The Post-traumatic Stress Disorder Checklist for DSM-5 or PCL-5) to determine the presence of stress disorder and chronic fatigue problems. A total of 120 patients were enrolled. The prevalence rate of fatigue symptoms was 17.5%. Twelve (10%) screened positive for chronic idiopathic fatigue (CIF), 6 (5%) for CFS-like with insufficient fatigue syndrome (CFSWIFS), and 3 (2.5%) for CFS. The mean total scores in PCL-5 were 9.27 ± 10.76 (range:0–44), and the prevalence rate of PTSD was 5.8%. There was no significant association after adjusting between CFS and PTSD, gender, comorbidities, and chloroquine phosphate administration. The obtained data revealed the prevalence of CFS among patients with COVID-19, which is almost similar to CFS prevalence in the general population. Moreover, PTSD in patients with COVID-19 is not associated with the increased risk of CFS. Our study suggested that medical institutions should pay attention to the psychological consequences of the COVID-19 outbreak.

Keywords COVID-19 · Chronic fatigue syndrome / myalgic encephalomyelitis · Post-traumatic stress disorder · Post-COVID morbidities

Introduction

Since the beginning of the novel coronavirus in China, it is noted that the long-term effects of the severe illness survivors remain unknown. As the virus pandemic is burning through the world and causing many mortalities and morbidities, researchers hypothesized that the COVID-19 could potentially cause post-viral complications, which may be lifelong and disabling (Perrin et al. 2020). Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)

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is one of the well-known complications of some viruses which presented with prolonged relapse of exhaustion, cognitive dysfunction, depression, and other symptoms after a minimal amount of activity (Carruthers et al. 2011). Previous data showed that many survivors following the SARS-COV-1 outbreak developed CFS / ME-like symptoms (Moldofsky and Patcai 2011). There is currently no generally accepted diagnostic method for CFS/ME, so it is first necessary to rule out any disorders with similar symptoms. The literature indicates that several potential causes play a role in the pathophysiology of the disorder, including hormonal disturbances, immune system dysfunction, infection, and nervous system abnormalities (Shephard 2001). The precise explanation for what causes post-viral-fatigue remains uncertain. However, studies on the coronavirus and the influenza virus epidemics have suggested that these agents can alter the immune response. Moreover, the pro-inflammatory cytokines such as interferon-gamma and interleukins are released following the viral infection, passing through the blood-brain barrier and affecting the central nervous system (CNS) organs such as the hypothalamus (Hives et al. 2017). The autonomic alteration consequence of hypothalamus involvement may result in cognitive abnormality, sleep/wake cycle dysregulation, profound fatigue, and myalgia in the long term in favor of CSF/ME (Carruthers et al. 2011). Post-traumatic stress disorder (PTSD) refers to a category of psychiatric conditions triggered by trauma or other life-stressing factors (Organization 1992). People with stress-related disorders might represent a group of physiological dysregulation due to altered immune profiles (Glaser and Kiecolt-Glaser 2005; Passos, Vasconcelos-Moreno et al. 2015; Speer et al. 2018). Prior data indicated a correlation between PTSD and several infectious diseases (Jiang et al. 2019). According to the literature, PTSD could occur after recovery from a life-threatening illness. PTSD prevalence rates for a life-threatening condition in an intensive care unit (ICU) is 14–59% (Wu et al. 2005). Moreover, our previous work showed that stress and anxiety increased the vulnerability of COVID-19 infection (Ramezani et al. 2020). However, studies on the role of stress-related disorder in major life-threatening infections are still limited.

In the present study, we aimed to determine the presence of long-term adverse effects resembling CFS/ME symptoms such as persistent fatigue and PTSD in COVID-19 remitted patients who had no history of previous psychiatric problems or receiving psychiatric drugs. Moreover, the prevalence and predisposing factors for experiencing the mentioned symptoms were evaluated. To the best of our knowledge, it is the first study to assess PTSD and CFS in COVID-19 patients.

Patients and method

Study setting and population

We evaluated all admitted patients diagnosed with COVID-19 between 20 February 2020 and 20 April 2020 ($n = 406$). History of previous medical and psychiatric illnesses, COVID-19 characteristics, viral markers, complete blood count, biochemistries, sedimentation rate, C-reactive protein was assessed. The exclusion criteria consisted of (1) patients who died at the hospital during the admission or in 6 months after the discharge; (2) patients infected with COVID-19 twice or more after discharge confirmed by positive polymerase chain reaction (PCR) test; (3) a history of previous influenza or any life-threatening infection (sepsis, endocarditis, and meningitis, or other central nervous system infections) before the diagnosis of COVID-19, (4) patients who have received psychiatric medication in the last year. These details and personal identifying information were stored. Out of 406 patients, 31 had no definitive diagnosis based on a spiral chest CT scan characteristics or positive COVID-PCR test and were removed from the study. Two hundred sixty-seven patients were eventually discharged, and 108 died. Eligible patients who had at least one negative PCR test during follow-up were contacted. At the time of the follow-up survey, 39 patients who declined to return to the hospital stated they were worried about COVID-reinfection. Twenty-seven residents in remote areas could not travel to our center due to lockdown. Nineteen patients died after discharge, and we failed to contact 35 patients by phone, in that they did not answer our phone call. The remainder had one of our exclusion criteria, so they were excluded, and ultimately, 120 patients were enrolled in our study (Fig. 1). All patients signed the informed consent forms and were evaluated by standard questionnaires at clinics 6 months after discharge. The study was approved by the ethical committee of the Shahid Beheshti University of Medical Science (IR.SBMU.RETECH.REC.1399. 104).

Screening questionnaire

CFS/EM symptoms' severity was analyzed using a previously validated questionnaire based on the Fukuda guidelines (Fukuda et al. 1994). Participants were asked to rate the severity of fatigue and the eight additional criteria over the past 6 months using an ordinal scale of 0 (no symptoms), 1 (trivial), 2 (mild), 3 (moderate), and 4 (severe). The fatigue severity and the sum of the eight ancillary criteria (Sum8) were evaluated. The fatigue severity scales and Sum8 scores divided the graph into four quadrants consist of healthy controls (HC: fatigue = none, trivial, or mild; Sum8 < 14), chronic idiopathic fatigue (CIF:

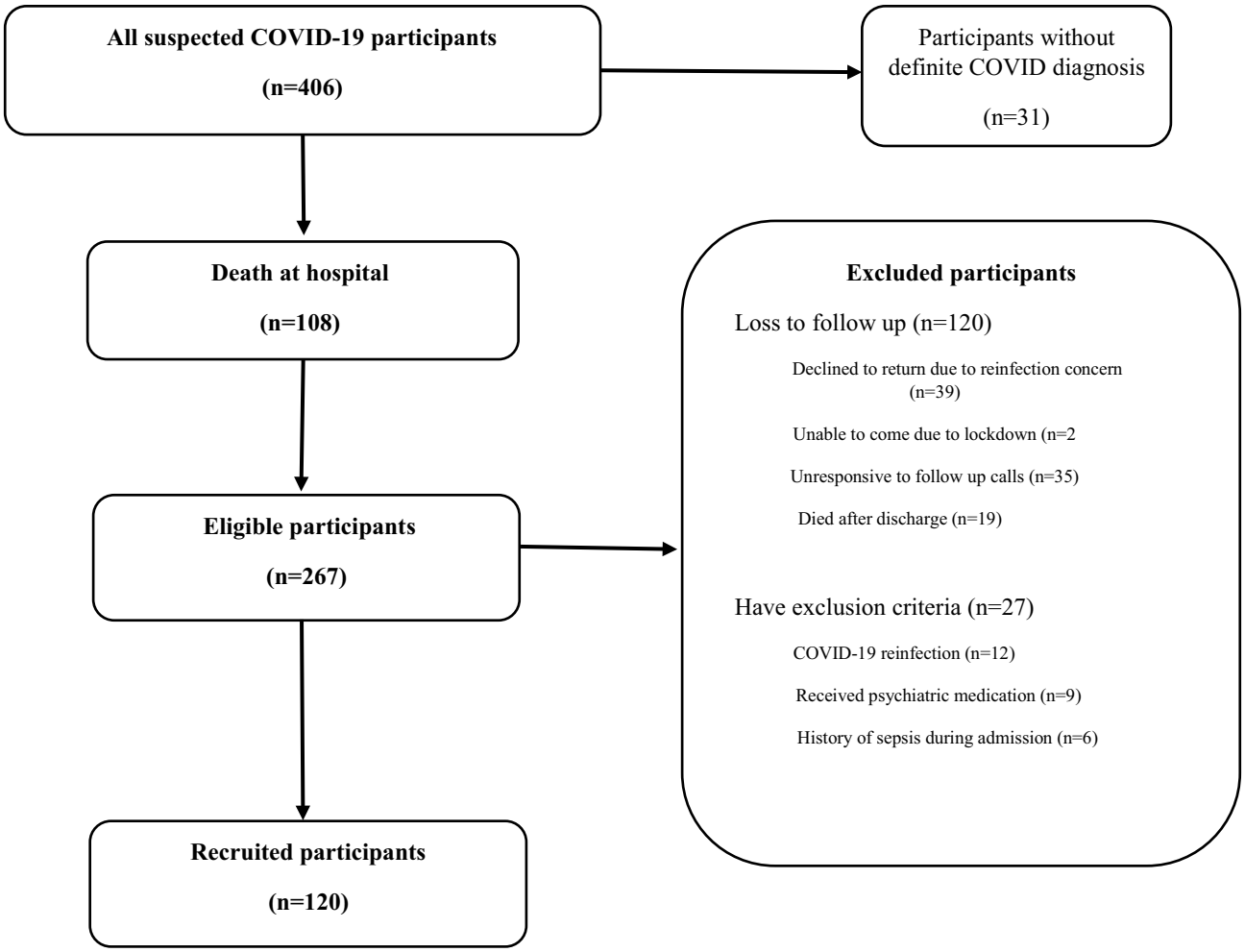

Fig. 1 Study selection flowchart

fatigue = moderate or severe; Sum8 < 14), CFS-like with insufficient fatigue syndrome (CFSLWIFS: fatigue = none, trivial, or mild; Sum8 ≥ 14), and chronic fatigue syndrome (CSF: fatigue = moderate or severe; Sum8 ≥ 14) (Baraniuk et al. 2013). The DSM-5 PTSD checklist (PCL-5) is a self-report assessment of 20 items that measure the presence and severity of PTSD symptoms (Weathers et al. 2013). It measures four symptom clusters B to E in DSM-5, including intrusion (five items; B), avoidance (two items; C), negative alterations in cognition and mood (seven items; D), and alterations in arousal and reactivity (six items; E). The items are rated from 0 (not at all) to 4 (extremely) and are summed for a total severity score. The total score ranges from 0 to 80, with a recommended cut-off of 33 for PTSD caseness (Blevins et al. 2015; Bovin et al. 2016). The Persian version of this scale was assessed in Iran for psychometric properties and yielded acceptable validity and reliability scores (Sadeghi et al. 2016).

Statistical analysis

All statistical analyses were performed using SSPS version 16.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables are expressed as absolute values (percentage), and continuous variables were expressed as mean value ± standard deviation. Multivariable logistic regression was used to adjust for confounders' effect when appropriate to determine independent associations of binary outcomes. The confidence interval of 95% was considered for the interpretation of the estimations.

Results

A total of 120 COVID-19 patients, 40 (33.3%) females and 80 (66.7) males, were included in our study. The mean age of patients was 54.62 ± 16.94 years. The mean length of hospital stay was 3.58 ± 2.52 days. The majority of the

Table 1 Baseline characteristics of study participants (120)

Characteristic	N(%)
Gender, (%)	
Female	40(33.3%)
Male	80(66.7%)
Age (Mean ± SD)	54.62 ± 16.94
Comorbidity	51(44.3%)
Medical History, n (%)	
Diabetes	28(23.3%)
Hypertension	32(26.7%)
Cardiovascular disease	20(16.7%)
Rheumatologic condition	2(1.7%)
COPD	6(5%)
Chronic liver disease	5(4.2%)
Malignancy	4(3.3%)
Hepatitis-B	5(4.2%)
Immunodeficiency	3(2.5%)
Fever ≥ 37.5	54(47%)
Shortness of breath Dyspnea	88(72.2%)
Anorexia	13(11.3%)
Myalgia	27(23.5%)
Headache	11(9.2%)
ICU admission	9(7.5%)
Length of hospital stay	3.58 ± 2.52
O2 Saturation Pulseoxymeter	87.5 ± 7.04
Laboratory test	
First WBC	8.09 ± 4.78
First Neutrophil percentage	75.09 ± 11.87
Lymphocyte Percentage	18.11 ± 10.59
ESR	46.45 ± 25.83
CRP	63.75 ± 41.80
Bilateral distribution	78(83.9%)
Unilateral distribution	1(1.1%)
Bilateral consolidation CT	14(15.1%)
Unilateral consolidation CT	1(1.1%)
Abnormalities on chest CT	91(97.8%)
Antibiotic	72(62.6%)
Drug regimen	
Monotherapy	9(7.9%)
Two drug	35(30.7%)
Three drug	49(43%)
Four drug	1(0.9%)
Oseltamivir	28(25%)
hydroxy_chloroquine	67(58.8%)
chloroquine phosphate	19(17%)
Kaletra	92(80%)
Ribavirin	52(45.2%)
Glucocorticoids therapy	3(2.6%)
Interferon_Beta_1a	10(9%)
Interferon_Beta_1b	9(8%)
PTSD	
PCL-5	9.27 ± 10.76
Positive	7(5.8%)

subjects had shortness of breath at the time of admission (72.2%); in addition, the most common comorbidity was hypertension (26.7%) (Table 1). The prevalence rate of CFS/ME was 21 (17.5%). While 99 (82.5%) respondents did not report any symptom within the preceding 6 months of the survey administration date, 12 (10%) reported CIF, 6 (5%) reported CFSLWIFS, and 3 (2.5%) reported CFS. Using our predefined cut-offs for the PTSD scoring system to screen the presence and severity of PTSD, we observed a total severity

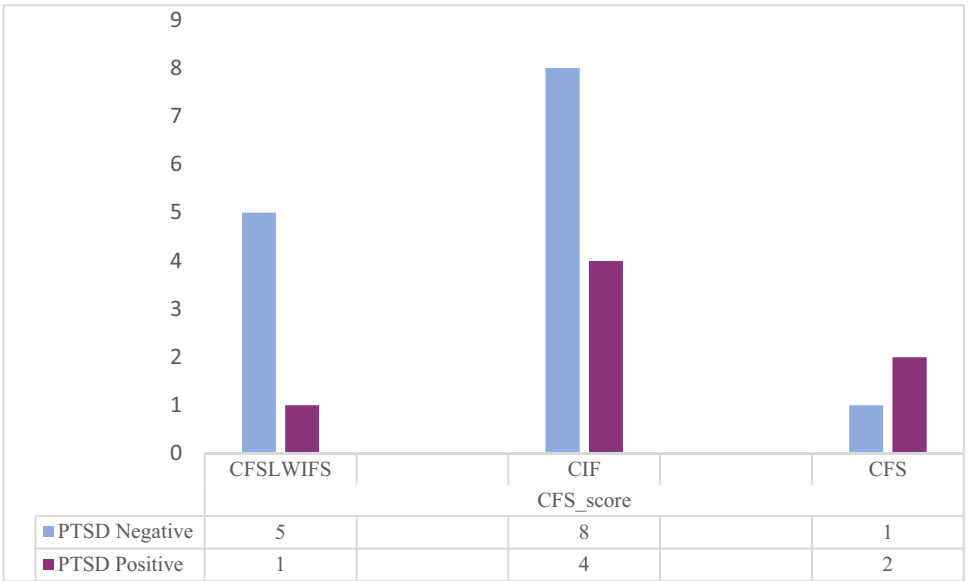

Fig. 2 Number of participants experiencing PTSD and CFS

Table 2 The estimation of Asthenia odds ratio for study-specific variables. Univariate & multivariate logistic regression for eight variables. Significant level < 0.05

Variable	Univariate			Multivariate		
	Odds ratio	95%CI	P-value	Odds ratio	95%CI	P-value
Sex	2.655	1.017–6.931	0.046	0.563	0.164–1.929	0.360
PTSD	1.552	1.237–1.948	0.001	2.341	0.700–1.963	0.999
Comorbidity	0.359	0.131–0.982	0.046	0.140	0.230–1.314	0.996
chloroquine phosphate	3.937	1.295–11.971	0.016	1.545	0.331–7.221	0.580

score in 7 (5.8%) study participants. The mean total score in PCL-5 was 9.27 ± 10.76 (range 0–44). Of the 7 participants who screened positive for PTSD, all (100%) of them were scored as CFSLWIFS 1 (14.3%), CIF 4 (57.1%), and CFS 2 (28.6%) (Fig. 2). According to univariate analysis, sex, PTSD, comorbidity, and chloroquine phosphate administration are significantly associated with asthenia score. Table 2 shows the logistic regression results for asthenia as the dependent variable and sex, PTSD, comorbidity, and chloroquine phosphate as independent variables. These variables did not reveal any significant predictive value for the severity and prevalence of asthenia in multivariate analysis.

Discussion

COVID-19 has affected many people throughout the world. In light of public health concerns about the COVID-19 infection's adverse effects, and according to the available evidence for SARS-COV-1 and H1N1 fatigue-related symptoms (Islam et al. 2020), we assessed the prevalence of CFS/EM following COVID-19 infection. This study found that 17.5% of patients experienced various fatigue levels; only 14.2% qualified for CFS criteria. According to the literature, CFS/EM prevalence rates following viral infections were varied by population group, case definitions, and diagnostic techniques (Lim et al. 2020).

Tansey et al. in their study, investigated survived patients following the SARS-COV-1 outbreak. They found that 64% of subjects reported fatigue and sleep disturbances at 3 months, while after 6 months and 12 months, the numbers were 54% and 60% (Tansey et al. 2007). In 2009, Lam et al. evaluated patients recovering from SARS in Hong Kong over 4 years. They noticed that 27.1% met the criteria for CFS/ME. Moreover, 42.5% had experienced at least one active psychiatric illness at the follow-up, and the most common problem was PTSD (54.5%) (Lam et al. 2009). In a case-control study, Moldofsky et al. examined people about 19 months after the onset of infection following the SARS outbreak. They demonstrated fatigue, myalgia and pain, depression, and sleep difficulties in subjects similar to post-febrile CFS symptoms. They also showed that only 2 of 22 patients had scores suggestive of PTSD (Moldofsky and Patcai 2011). In addition, earlier post-H1N1 pandemic experiments had similar findings. A study by Magnus et al. about the H1N1 pandemic in Norway suggested that H1N1 infection was associated with an increased CFS/EM risk more than twofold. Moreover, the younger population would be at more risk for post-infection CFS/EM (Magnus et al. 2015). Our study demonstrated that the measured CFS prevalence following COVID-19 is 2.5% (3 out of 120); on the other hand, the estimated prevalence of chronic fatigue syndrome in a general population using the Fukuda criteria is around 2% (Baraniuk 2017). Therefore, there is well within this ballpark of population prevalence. This finding would suggest that the contribution of COVID-19 disease to the future risk of CFS is minimal.

We showed 5.8% of subjects suffered from PTSD after 6 months of infection onset. A systematic analysis of the psychological consequences of SARS and the H1N1 pandemic indicated that the average prevalence of PTSD among healthcare workers (HCWs) was approximately 21% (Vyas et al. 2016). However, this proportion was variable among the general population following the infectious disease outbreak (Lam et al. 2009; Vyas et al. 2016).

We noticed that variables such as oxygen saturation at the time of admission, primary symptoms, admission in the ICU, and lab test parameters were not associated with asthenia occurrence. Female sex was associated with an increased risk of CFS/ME. This finding is in line with the previous data, which showed that women are susceptible to CFS/ME approximately 1.5- to 2-fold higher than men (Lim et al. 2020). However, after adjustment, the mentioned result did not remain.

Our study has several limitations. The sample size was small because many survivors were reluctant to attend the hospital. Patients' premorbid psychiatric status was not documented; additionally, we did not evaluate the patients' depression and quality of life scores at the survey time, which may cause some of the functional limitations. We assessed patients only for 6 months post-discharge; no special groups such as HCW enrolled in our study. Therefore, further study with a larger sample size, including ethnically and professionally diverse groups and longer follow-up duration, should be accomplished.

Conclusion

Our findings illustrated the incidence of CFS/EM and associated factors in non-HCW COVID-19 recovered participants. This is the first study to discover the long-term psychological adverse effects in COVID patients. Considering CFS/ME clinical heterogeneity, longitudinal and standardized studies to determine CFS/ME courses with treatment intervention and follow-up assessments are recommended.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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