MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 9(8) pp. 325-331, August, 2021
Available online http://www.meritresearchjournals.org/mms/index.htm

DOI: 10.5281/zenodo.5208019

Original Research Article

Risk Factors and Characterization of Post-COVID-19 Syndrome, in Jordan

Mohamad-Said Almasri[1], Rashed Alqaisi[1], Mohammad Al-Shagahin[1], Prof. Dr. Waqar Al-Kubaisy[1*], Dr. Ahmad Aljarajreh[1], Prof. Dr. Hani Al-Shagahin[1]

Faculty of medicine, Mutah university, Karak, Jordan[1]

***Corresponding Author's E-mail: waqar_abd@yahoo.co.uk**
Phone number: +962780858405

Abstract

Controversial information about the sequelae of COVID-19 after recovery or post-COVID-19 syndrome (PCS). Whereas considerable studies have been done on COVID-19, proportionally, scarcity of literature addressing the PCS, particularly the risk factors causing this syndrome. Determining the prevalence, most common manifestations of PCS, and the possible related risk factors is an important issue. A cross-sectional, online questionnaire-based study was conducted. This questionnaire was posted to the Association of "My experience with COVID-19" in Jordan. Socio-demographic, as well as COVID 19 illness information was collected, from 657 COVID-19 recovered patients at least three months after illness started. PCS prevalence was 71.9%, where the patient experienced, at least one PCS symptom. Most common symptoms including dyspnoea, fatigue, test and smell impairment, cough, and depression. Six factors were found to be significantly increasing the risk of PCS (using OR, 95% CI); female (2.06, 1.409-2.856), aging ≥30 (1.64, 1.16-2.33), DM (2.978, 1.08-8.21) hypertension, (2.22, 1.118-4.423), respiratory disease (2.33, 1.21-4.501), and neuro-psychological disturbance during illness (3.79, 2.574 - 5.573). Those patients showed also a significantly higher rate of post-COVID-19 syndrome than their counter groups. Therefore, females, aging ≥30, comorbidity, and neuropsychological disturbance during illness, are considered as a risk group for PCS. Thus, psychological and medical support is highly recommended during and after the episode particularly for the risk groups.

Keywords: Post COVID-19 syndrome, Long COVID-19, Post-Acute Sequelae of SARS-CoV-2 infection, long haul, long COVID-19, Chronic COVID-19 syndrome, epidemiology, risk factors, symptoms, Jordan

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak, which was caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), it began in Wuhan, China, but rapidly has been spread all over the world. Thus, in March 2020 the World Health Organization (WHO) has announced it as a pandemic (World Health Organization, 2020). For that reason, it is difficult for anybody to think that this disease might be a chronic form. Interestingly the term post-COVID-19 syndrome (PCS), long COVID-19 or long-haul COVID-19 was started to be used by the scientific and medical communities. Various forms of post-COVID syndrome have already been proposed, and the most common form is symptoms lasting for more than three months after the first symptom onset (Callard et al., 2021). Whereas there is lacking the exact definition, several authors identified that the most

frequent symptoms of post-COVID are fatigue, dyspnoea, cognitive and mental disorders, headache, myalgia, chest and joint pain, smell and test dysfunctions, cough, alopecia, insomnia, sputum, and less common symptoms of, chills, flushing, ear pain and visual impairment. These symptoms may persist for up to six months and counting after hospital discharge or symptom onset (Stavem et al., 2021; Xiong et al., 2021; McMahon et al., 2021). According to the National Institutes of Health This illustrates the multifaceted nature of post-COVID-19 that involves multiple organ systems. (NIH 2021). Moreover, several studies have also reported different persistent symptoms in frequencies and durations among post-COVID-19 survivors (Bellan et al., 2021; Carfi et al., 2020; Cirulli et al., 2020; Davis et al., 2020). This may be due to characteristics study sample, and data collection methods in each study or the heterogeneous condition of the post-COVID-19. In another words the precise symptomatic manifestations of post-COVID-19 remains elusive and may involve multiple subtypes or phenotypes (Yong, 2021). However, it is obvious, that a new wave of chronic condition has been brought by the COVID, known as long COVID, that merit serious attention from medical scientific and social point of view to resolve. ShinJie Yong in his literature review stated that at least 10% of COVID-19 survivors develop long COVID, which is likely underestimated (Yong, 2021). Interestingly, globally it is estimated that 17.5 million people are facing post-COVID-19 (Altmann, 2021).

While large numbers of studies have been made on the acute phase of COVID-19, in Jordan, no study was done on the post-COVID-19. Therefore, the current study, try to fulfil these gaps. Hence, the aim of this study was to detect the prevalence and the risk factors for the development of the post-COVID-19 syndrome (PCS)as well to identify the symptoms and their relation to the socio-demographic and medical characteristics of patients who survived COVID-19 after more than three months from onset of illness in all over Jordan

MATERIAL AND METHODS

A cross-sectional self-administered-online based questionnaire study, was conducted, involving 657 patients recovered of COVID-19, illness. The enrolment of those patients was from all governorates of Jordan. The inclusion criteria were patient aged ≥ 18 years old, with at least three months from the onset of illness, and confirmed negative PCR. We exclude patients who had a history of neurological or psychiatric disease prior to the COVID-19 infection. First of all, a questionnaire was translated into Arabic, and converted into a web-based survey using Google Forms Application.

By the online questionnaire, consent was obtained from each participant. At the very beginning of the questionnaire, it has been clarified that respondent must be aged ≥ 18 years old, with at least three months from the onset of illness, and confirmed negative PCR. The questionnaire link was posted to the potential members of “My experience with COVID-19” group by using common social media like Facebook, WhatsApp, Instagram, and Twitter; thereafter the members who clicked the link were directed to the Google forms. This "My experience with COVID-19” Group has been created in October 2020 which is composed of almost 28000 COVID-19 recovered individuals from this illness(My Experience with Corona 2020). To minimize the missing data, the participants were requested to fill all the items in the online questionnaire otherwise could not proceed to the next page; a notification box indicating a warning note that one or more items were not answered. On completion of the questionnaire, the participants were directed to clicks the submit option and finally, the online questionnaire was sent to the drive. In the cover letter of the web-based survey, the participants were informed about the purpose of the study, ensure confidentiality, and the voluntary nature of the study; the possibility of withdrawing from the study at any time was emphasized. They also assured that their non-participation or withdrawal from the study will not affect their current or future relationship with the health care services.

The used questionnaire. consists of two parts. The first part related to, socio-demographic data (age, sex, BMI …etc.) and data about theCOVID-19 status and other comorbidities of the person (Severity of the disease and presence of other diseases) While the second part, related to post-COVID-19 manifestations.

After six weeks, of data collection, a total number of 657 questionnaires were obtained from the participants. For the purpose of consistency, data entry into the SPSS software version 21 was done. Data cleaning was carried out Data analysis was carried out, descriptive statistics were performed (mean and standard deviation, frequency, and percentage). Inferential statistics was applied by using the chi-square test and odds ratio. The p-value of <0.05 was considered significant.

RESULTS

Sociodemographic and clinical Characteristics

The mean age of 657 COVID-19 recovered patients, was 30.55 ± 11.9 years, with a range of 15-78 years old. Only 20 (3%) have had a history of hospital admission during their COVID-19 illness, and 118 (18%) patients were smokers. Females constituted 444 (67.6%), 23 of them were pregnant. Most patients (77%.6) had at least one psychological symptom during illness. Regarding the comorbidity diseases, there were 29 (4.4%) Diabetes mellitus, 42 (6.4%) hypertension, and 44(6.7%)

Table 1. Sociodemographic and clinical Characteristics of 657 COVID-19 recovered patients in Jordan 2020-2021

Characteristics	Numbers (%)	PCS patients N(%)	χ2	P value
Gender				
Male	213(33.4)	132 (62)	15.178	0.001
Female	444(67.6)	340 (76.6)		
Age*				
<30	363(55.5)	245 (67.5)	7.714	0.005
>30	291(45.5)	225(77.3)		
BMI*				
≤18.499	30 (4.6)	21(70)	4.562	0.102
18.5 -24.99	265 (40.3)	180(67.9)		
≥25	330 (50.2)	250 (75.8)		
Hospitalized	20 (3)	17(85)	1.766	0.184
Smoking	118(18)	80(67.8)	1.161	0.281
Neuropsychological symptom during illness	510 (77.6)	400(78.4)	48.929	0.001
Pregnant females	23 (5.6)	16(69.6)	0.536	0.463

BMI*: 32 out of patients couldn't confirm their height and weight
Age*: three out of 657 patients didn't answer the question regarding age

respiratory disease patients (Table 1).

Significantly, a higher rate of PCS among females (76.6%) was detected compared to males (62%), $\chi 2$ = 15.178, P<0.001. Additionally, being a female, be at a significantly two times higher risk than a male to have PCS, OR=2.006, 95% CI 1.409-2.856. By categorizing the participant's age into; younger than 30 years old, and 30 years and more (≥30), groups. Interestingly, those participants who were ≥30 years old, showed a significantly higher rate of (77.3%) of PCS, than their counter group (67.5%), $\chi 2$=7.714, P=0.005. Moreover, those patients showed more than one and a half times, OR =1.64, 95%, CI= 1.16-2.33, significantly higher risk for PCS development, than the younger group.

Astonishingly, the 400 patients, who had psychological symptoms during the COVID 19 illness, showed significantly a higher rate (78.4%) of PCS, than those 72 (48.9%) patients who had no such symptoms. $\chi 2$=48.929, P<0.001. Moreover, we gave evidence, that patients who had complained of psychological symptoms during the COVID 19 illness, being at almost four times more significant risk of developing PCS (OR= 3.79, 95% CI = 2.574 - 5.573) compared to those who had no psychological symptoms.

Interestingly, of the 18 recorded post-COVID-19 symptoms, eight were new symptoms, which is either just appeared or reappeared, after the disappearance. The remaining 10 are persistent symptoms that had appeared during COVID19 illness.

Table 2 exhibited the frequency of these symptoms in descending order. More than one-third (35.8%. 35.6%) of long COVID patients complaining of; taste and/or smell impairment and fatigue, including35 and 42 new cases respectively. almost one-quarter, (24.8%, 24.6%, and 24.1%), complaining of, joint pain, cough, or depression, including 31, 43, and 20 new cases respectively. On the other hand, 26.7%, 15.9%, 15.7%, 14.4%, 13.3%, 10.6%, 9.7%, 5.9%, 4%, and 3.2% had persistence symptoms of chest pain, hair loss, sour throat, memory problems, ear pain, diarrhoea, chills, visual impairment, eye itching and vomiting respectively.

In order to detect whether any comorbidity (DM, hypertension, and respiratory diseases), among COVID19 patients, acts as a risk factor for the development of PCS. We detected that DM patients who were infected with COVID-19 have a significantly higher rate of PCS, particularly, the symptoms of; eye itching, ($\chi 2$=5.985, P=0.014), vomiting ($\chi 2$ =17.98, p<0.001), and chills ($\chi 2$=4.869, P= 0.027). Furthermore, we have detected that DM patient during the PCS period is significantly at a higher risk of having, eye itching, almost three times (OR 2.978, 95% CI 1.08-8.21), vomiting nine times (OR8.96, 95% CI 2.66-30.1), and chills, four and half times (OR4.41, 95% CI 1.2-16) than non-diabetic patients.

Significantly higher rate of PCS symptoms like; cough (31.0%, P=0.02) vomiting (7.1%, P=0.03), vision disturbance (14.3%, P = 0.001), and eye itching (9.5%, P = 0.008), were detected among the hypertensive patients, compared to normotensive. Moreover, during the PCS period, the hypertensive patient is significantly at risk of having, more than two times of cough (OR2.224, 95% CI 1.118-4.423), almost four times of vomiting (OR3.859, 95% CI 1.045-14.24), four and a half times vision disturbance (OR4.485 95% CI 1.71-11.75) and more than four times of eye itching (OR4.204, 95% CI 1. 33-13.28), then normotensive patients.

The comorbidity of COVID19 infection with the respi-

Table 2. Persistent and New Symptoms of 472 Patients with post-COVID-19 Syndrome in Jordan 2020-2021

Post-COVID-19 symptoms	Total Cases N (%) =472	Persistent cases N(%)	New cases
Taste and smell dysfunction	169 (35.8)	134 (79)	35 (21)
Fatigue	168 (35.6)	126(75)	42 (25)
Shortness of breath	145 (30.7)	99 (68)	46 (32)
Headache	143 (30.2)	109 (76)	34(24)
Chest pain	126 (26.7)	126(100)	-
Jointpain	117 (24.8)	86 (74)	31(26)
Cough	116 (24.6)	73 (63)	43(37)
Depression	114 (24.1)	94 (82)	20 (18)
Anxiety	104 (22)	99 (95)	5 (5)
Hair loss	75 (15.9)	75 (100)	-
Sour throat	74 (15.7)	74(100)	-
Memory problems	68 (14.4)	68(100)	-
Ear pain	63 (13.3)	63(100)	-
Diarrhoea	50 (10.6)	50(100)	-
Chills	46 (9.7)	46(100)	-
Visual impairment	28 (5.9)	28(100)	-
Eye itching	19 (4)	19(100)	-
Vomiting	15 (3.2)	15(100)	-

Table 3. Relation of the presence of Co-morbidities, with the appearance of PCS symptoms

PCS Symptoms	Diabetic N=29	Non-diabetic	Hypertensive N=42	Normotensive	Respiratory diseased N=44	Non-respiratory diseased
Vomiting	4(13.8%)	11(1.8%)	3(7.1%)	12(2%)	4(9.1%)	11(1.8)
χ2 (P value)	17.98 (0.001)		4.736 (0.03)		9.773 (0.002)	
OR(95% CI)	8.96 (2.66-30.1)		3.856 (1.045-14.24)		5.464(1.65-17.92)	
Eye itching	3(10.3%)	16(2.6%)	4(9.5%)	15(2.4%)	1(2.3%)	18(2.9%)
χ2 (P value)	5.985 (0.014)		7.008 (0.008)		0.065 (0.798)	
OR(95% CI)	4.203(1.33-13.28)		4.203(1.33-13.28)		0.767(0.100-5.886)	
Chills	24(82.%)	448(71.8%)	3(7.1%)	43(7.0%)	4(9.1%)	42(6.9%)
χ2, P value	4.869 (0.027)		0.001 (0.973)		0.313 (0.576)	
OR(95% CI)	4.406(1.2-16)		1.021(0.303-3.441)		1.357(0.463-3.975)	
Cough	9(31%)	107(17%)	13(31%)	103(16.8%)	10(22.7%)	106(17.3%)
χ2 (P value)	3.716 (0.054)		5.42 (0.02)		0.824 (0.364)	
OR(95% CI)	2.187(0.969-4.934)		2.224(1.118-4.423)		1.404(0.673-2.929)	
Visual disturbance	3(10.3%)	25(4%)	6(14.3%)	22(3.6%)	3(6.8%)	25(4.1%)
χ2 (P value)	2.742 (0.098)		11.02 (0.001)		0.750 (0.386)	
OR(95% CI)	2.778(0.788-9.798)		4.485 (1.71-11.75)		1.718(0.498-5.929)	
Chest pain	6(20.7%)	120(19%)	11(26.2%)	115(18.7%)	15(34.1%)	111(18.1%)
χ2, (P value)	0.043, (0.836)		1.41 (0.235)		6.733(0.009)	
OR,(95% CI)	1.102(0.439-2.766)		1.540 (0.752-3.154)		2.335(1.21-4.501)	

ratory diseases, showed a significantly higher rate of PCS symptoms, particularly, chest pain (χ2=5.733, P=0.009) and vomiting (χ2=9.773, P=0.002), Meanwhile, we gave evidence, that respiratory diseased patients are, at significant risk of having, chest pain more than two times (OR = 2.335, 95% CI 1.21-4.501) and vomiting, almost five and half times, (OR= 5.464, 1.65-17.92) during the PCS period of COVID19 illness than the respiratory diseased free patients from respiratory diseases (Table 3).

In concern to BMI, by classifying the BMI into; underweight (<18.5), normal weight (18.5–24.9), and overweight (≥25). We found the normal BMI patients showed a lower rate (67.9%) of PCS than those with the

overweight (75.8%) or underweight (70.0%). However, this variation was not significant (P= 0.102). On the other hand, no significant association was detected between the development of PCS and smoking ($\chi2$=1.161, P=0.28), pregnancy ($\chi2$=0.536, P=0.463), and history of hospitalization ($\chi2$=1.766, P=0.184). shown table (1)

DISCUSSION

While large numbers of studies have been made on the acute phase of COVID-19, on the other hand, proportionally a small number was done in studying long COVID or post-COVID-19 syndrome. The high prevalence (71.8%) that we found in our study representing a patient who has at least one physical or psychological symptom after three months or more, from the onset of the disease. These symptoms appear either as a new or as persistent from the acute phase. This finding supports the prospective cohort study in Wuhan, which found 76% of the patients reported at least one symptom, six months after illness onset (Huang et al., 2021). On the other hand, a study was done in the UK by The Office for National Statistics (ONS) on post-COVID-19 in December 2020, estimated that about 20% and 10% of COVID-19 patients, exhibited at least one symptom for 5 weeks and 12 weeks or longer respectively (Office for national statics, 2020). Moreover, a prospective cohort study done reported that 27.8% of COVID-19 patients were found to have at least one symptom after four months (Max et al., 2021).

Variation in the prevalence of PCS symptoms among all these studies in different countries may be related to the study type, study population, and health care services. In addition, the education and culture of the participants may play a role. Very few studies discussed the appearance of new symptoms after recovery. Our study found that 14.5% of COVID-19 patients complained of the appearance of new symptoms 3 months or more after the onset of disease. A higher rate (24.1%) of PCS newly symptoms (alopecia) was detected in Japan (Yusuke 2020). These differences in rates could be attributed to the difference in the age and gender of the study group. The appearance of new symptoms could be caused as a result of a new wave variant of the same virus, or other infection. Thus more studies are recommended to investigate this issue. In contracts with (Bodunrin et al., 2021), who couldn't find any association between a patient's age and the presence of persistent COVID-19, we have detected a significantly higher PCS rate among patients ageing≥30 years old. This is in alignment with Jennifer et al. (2021) study which reported, with the increasing age of the patient, the rate of PCS symptoms be increased. Similarly, Carole et al. (2021), detected that persistent symptoms for more than one month were significantly (P < 0.0005) associated with age, rising from 9.9% in the individuals aged 18–49 years to 21.9% in those aged ≥70 years. This means that an old age person is more prone to have PCS. Therefore, old age patients should be considered as a significant risk group of people, for the development of PCS, particularly we have confirmed this issue in our study (OR=1.64). An explanation for this could be that comorbidity is more prevalent among the old age group, which we also detected that comorbidity is a risk factor for particular symptoms in the PCS period. Another explanation might be related to the low immunity of elderly people, thus they are more likely to acquire other viruses during COVID-19 illness, or after recovering. Besides, that elderly people may give more attention to their health than the young. This study revealed that the rate of PCS differed significantly according to the patients' gender, where female patients showed a higher rate of PCS. This finding is consistent with what was reported by Carole et al. (2021). Several authors have found a higher the rate of long COVID symptoms in females few months after hospital discharge (Huang et al., 2021; Simani et al., 2021; Poyraz et al., 2020; Halpin et al., 2021; Sigfrid et al., 2021). Additionally, we gave evidence that, being a female, significantly having two times higher risk of developing PCS. This could be related to the Arabic culture and norms, since females do more effort for taking care of the family when sick. No significant association was detected regarding the history of hospitalization with the development of PCS, but the hospitalized COVID-19 patients, showed insignificant higher rates of PCS. Most probably could be related to the severity of the disease and are more prone to psychological symptoms that showed to have an effect on the post-acute phase. The manifestation of at least 10 symptoms during acute COVID-19 was found as a risk factor for long COVID-19 in a four-month follow-up study of COVID-19 survivors (Stavem,2021), Most studies did not find any association between long COVID-19 and initial disease severity during the acute episode. (Yusuke et al,2020, Townsend,2020). The COVID-19 patients with comorbidity (DM, hypertension, and respiratory) were significantly more liable to develop PCS, particularly of eye problems, vomiting, chest pain, cough, and chills. These findings were in agreement with Iqbal et al. (2021) and Marwa et al. (2020). Moreover, strong evidence was given from this study that patient who complained of neuropsychological symptoms during the COVID-19 illness, being at almost four times significant risk of developing PCS more than those who have no psychological symptoms, in concordance with Stavem et al. (2021) who reported that confusion and depression during acute COVID-19, associated with persistent fatigue during the PCS period Beside that Townsend et al. (2020) revealed that COVID-19 survivors with a history of anxiety or depression diagnosis or antidepressant were more likely to develop persistent

fatigue at 10-week post-discharge. Similarly, other studies of COVID-19 survivors reported prior psychiatric disorder as a risk factor for developing persistent symptoms (Yong 2021). Blerina et al., (2017)in their study shows how important is the psychological state of the patients as a risk factor, they reported that the levels of depression in patients reduce the odds of recovery from a disease. A lot of studies have reported that the severity of COVID-19 illnesses is significantly related to the higher BMI of the patient (Hamer, 2020, Huang 2020). Unfortunately, no study could be found investigating the relation between BMI and PCS. However, we found those, overweight and underweight persons having a higher rate of PCS than those with a normal BMI, but not significant. The results of this study could be explained by the fact, that the height and body weight was recorded by the responder him/herself, not by researcher-active measurement. Another possible explanation could be related, that most of the patients during the episode of COVID-19 were suffered from loss of appetite, loss of taste, diarrhoea, and vomiting which may lead to reducing the body weight.

CONCLUSION

The PCS prevalence, (71.8%) is high in Jordan. Particularly among certain populations like females, age ≥30 years, having neuropsychological disturbance during illness and comorbidity; DM, hypertension, and respiratory diseases. Those, who showed significantly higher risk factors for the development of PCS manifestation. In other words, those populations should be considered as a risk group for PCS occurrence. Therefore, the COVID-19 infection treatment is not only during the episode but has to continue several months after the recovery of the patient. Besides that, the PCS period will require not only scientific study and investigation but also needs early interventions including rehabilitation. Therefore, now we have to start steps in preparing for this unavoidable problem to improve the health care system and enhance the management of patients during the PCS period.

ACKNOWLEDGEMENT

The authors would like to express their gratitude and acknowledgment to all COVID-19 survivors enrolled in this study, who cooperated with us to conduct the interviews with them. The authors extend their acknowledgement to; Ghazi Majali, Ahmad Jurieh, Abedalaziz Alzu'bi, Husam Dais, and Areen Alfalayleh for their assistance in data collection and analysis. Additionally, great appreciation be given to the ethical committee in the Faculty of Medicine, Mutah University, for providing us with the approvement of this study

Conflict of interest

The Authors declares that there is no conflict of interest

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