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The associations of long-COVID symptoms, clinical characteristics and affective psychological constructs in a non-hospitalized cohort

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ABSTRACT

Objective: The effects of COVID-19, especially long-COVID, on the psychological health is incompletely understood. We aimed to evaluate the mid-term associations of the long-COVID symptoms and affective factors in a cohort of non-hospitalized patients. *Method:* A total of 166 patients were enrolled in this study, including 119 sedentary/non-athlete and 47 athlete subjects at the Post-COVID Outpatient Clinic of Semmelweis University. Clinical data regarding acute and long-term symptoms were obtained and detailed laboratory testing was carried out. Demographic data and psychological tests were collected. *Results:* We found a positive association between the level of depressive symptoms and anxiety and long-COVID symptom count, while life satisfaction and social support correlated negatively with the long-COVID symptom count. Higher haemoglobin levels and lower LDL-cholesterol were also shown to be moderating factors. A regression model showed that symptoms during acute infection, depression, age, and life

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satisfaction are predictors of the long-COVID symptom count. The presence of pre-existing affective or anxiety problems was also associated with higher reported long-COVID symptom count. Furthermore, we found significant association between pre-existing mental health problems and the investigated psychological constructs. *Conclusion:* It appears that long COVID-19 is associated with acute symptoms and mental factors. Depression and anxiety have been shown to have a negative effect on symptom perception, and also contribute to a higher number of symptoms in a non-hospitalized sample. Our study suggests bi-directional interconnection between clinical and psychological factors.

KEYWORDS

COVID-19, affective symptoms, perceived social support, PTSD, blood test

INTRODUCTION

In 2019 from Wuhan, China, a novel infectious disease called COVID-19 caused by the SARS-COV-2 virus has spread rapidly. Over 273,000 000 cases had been confirmed by the end of 2021 [1]. To date the primary focus of psychological research was on the descriptive assessment of mental disorders, post traumatic stress disorder (PTSD), anxiety and depression affecting COVID-19 patient. In addition, the studies investigated mostly hospitalized patients, particularly those in the Intensive Care Unit (ICU), conversely only a small margin of studies concentrated on non-hospitalized COVID-19 patients [2].

Depression, anxiety and PTSD are the most common mental problems the patients face after COVID-19 [3–5]. According to Poyraz et al. [3] 25.4% of those formerly infected suffer from moderate to severe PTSD symptoms. Grey et al. [6] found that those people who perceived high social support reported lower levels of depression, irritability, and loneliness than people with a lower level of perceived social support.

Perception makes us able to experience ourselves, our existence, our environment and others, but unfortunately, it is often biased. Illness perception is a cognitive appraisal and a unique interpretation of the patient's illness and its possible outcomes [7]. This mental construct includes one's attitude concerning the illness, personal beliefs and fears and through this process creates a cognitive framework [8]. The representation develops as soon as the patient is informed of the diagnosis and it evokes emotions in ourselves. A variety of factors play a central role in this dynamic process, such as past knowledge of the disease, prior experiences, personality traits (e.g., neuroticism), and physical health [9, 10]. Symptom perception hypothesis states, that people with negative affectivity (such as depression or anxiety) tend to report more symptoms and experience them more severe despite objective medical evidence to the contrary [9]. It has also been well studied that negative affectivity and neuroticism may lead to an inflated perception of symptoms, in which people with illnesses build a peculiar pattern or interpretation framework based on their understanding of the disease, as well as their prior experiences [9]. It happens the same way in case of a virus-infection, such as COVID-19.

Specific biological markers have also been proven to be positively correlated with mental illness, mainly affective disorders. Biological markers such as C Reactive Protein (CRP), LDL cholesterol (LDL-C) and haemoglobin (HGB) were investigated in connection to affective disorders. Higher levels of CRP were associated with the severity of overall depression [11]. LDL-C

level was also found to be higher in people with major depressive episodes [12]. Hemoglobin and ferritin levels were also investigated in certain populations. Low level of these biological markers was associated with depressive symptoms [13, 14]. These associations are important as recent studies found that the altered levels of these biological markers might be risk factors of COVID-19, or they might affect or predict the severity of the infection [15–18].

Different studies distinguish between long-COVID based on the involved time interval. NICE [19] guidelines define "ongoing symptomatic COVID-19" within 4–12 weeks after the commencement of the infection. Post-COVID syndrome is a set of symptoms that persist or develop after 12 weeks of COVID-19. In clinical terminology „long-COVID" includes both of these forms. Several studies reviewed our knowledge about long-COVID and they have found that the most frequent physiological symptoms are the following: fatigue, dyspnea, cardiovascular dysfunctions, olfactory and gustatory dysfunction, weakness, joint pain, myalgia. Regardless of whether the patient is hospitalized or not, these conditions can develop or persist.

The presence of comorbidities, higher age and male sex are known risk factors in terms of mortality in COVID-19: in a meta-analysis of 20 studies aged>50 years, concomitant cardiovascular, cerebrovascular, hypertension and diabetes carried significantly higher risk ratios [20]. Not only mortality, but the risk to develop long-COVID symptoms increases with age, concomitant asthma, lung disease, heart disease and even the number of symptoms in the first week play a significant role [20]. Identifying those non-hospitalized individuals who are at risk of developing mental issues after COVID-19 is of great importance.

Importantly, the vast majority of SARS-CoV-2 infected patients do not present with severe symptoms mandating hospitalization. Therefore, the concerning data is sparse as the largest affected groups have not been investigated satisfactorily so far. Consequently, in this study, our aim was to evaluate the mid-term associations of the long-COVID and affective factors in a non-hospitalized subjects. Besides the associations between the long-COVID and affective factors, we intended to find constructs that might moderate the presumed positive relationship between the worsened mental health status and the long-COVID symptoms.

MATERIALS AND METHODS

Subjects presenting between March 2021 and December 2021 at the Post-COVID Outpatient Clinic of the Heart and Vascular Center of Semmelweis University were invited to participate in the study. Exclusion criteria were insufficient medical records and/or psychological testing, >18 years of age. The study population included athletes and non-athlete individuals. The sports cardiology team at the SE Heart and Vascular Center regularly performs cardiovascular screening among highly trained athletes playing at national, international and olympic levels, including return-to-play examinations after COVID-19. The diagnosis of COVID-19 was confirmed by PCR, rapid antigen test or antibody level measurement in all subjects. The testing protocol comprised the same modalities for both athlete and non-athlete groups: patient history, physical examination, 12-lead ECG, and blood tests. Athletes were invited for an optional control examination after returning to play or presented due to long-term symptoms. The non-athlete patients visited our Post-COVID Outpatient Clinic on their initiative due to their anxiety or prolonged symptoms. Hungarian Medical Research Council approved the study (approval number: IV/9697-1/2020/EKU) and participants signed the informed consent form.

Measures

Baseline characteristics (sex, age) and medical history were retrieved from institutional medical records (Medsol). All psychological and more granular decription of demographic data (relationship status, education, monthly income, and residence) were ascertained using targeted questionnaires.

Long-COVID symptoms

Based on the theory of the illness and symptom representation models, our main focus was to investigate the nature of symptom count, thus our dependent variable was the self-reported symptom count. In our study the accepted long-COVID symptoms corresponded to the most common long-COVID symptoms according to the international and Hungarian experiences [2, 21, 22]: fever, weakness, anosmia and ageusia, chest pain, upper respiratory symptoms, headache, gastrointestinal symptoms, dyspnoe and muscle or joint pain. In order to analyze the symptoms cumulative nature and significance, we created a score by adding up the number of symptoms reported by the patients regardless of their severity.

MEASURES OF PSYCHOLOGICAL HEALTH

History of mental health problems

The history of mental difficulties (depression, anxiety, OCD, panic, phobia and others) were assessed by self-reported questionnaire.

Beck-Depression Inventory (BDI)

We used the validated Hungarian version of the shortened Beck-Depression Inventory [23]. The 9-item self-report instrument describes clinical manifestations of depressive symptoms. Patients are asked to indicate the frequency of their symptoms on a numerical scale ranging from 1 to 4. The test defines the severity as follows: 0-9 points normal range, 10-18 as mild depressive state, 19-25 as moderate depression, and 25 or over as severe depression (Cronbach-alpha = 0.835).

Beck Anxiety Inventory (BAI)

The Hungarian validation of the Beck Anxiety Inventory was used to measure state anxiety [24]. This 21-item tool assesses the clinical symptoms of anxiety, including cognitive, physical, and psychological factors (Cronbach alpha: 0.949).

Life satisfaction (LS)

A 10-point Likert scale was used to measure life satisfaction (completely unsatisfied to completely satisfied). The 1-item tests proved to be reliable and valid especially in well-being studies [25].

Multidimensional Scale of Perceived Social Support (MSPSS)

The Hungarian Validation of the Multidimensional Scale of Perceived Social Support questionnaire was used to assess social support for the participants [26]. The higher the score

achieved on this 12 item-tool, the greater the significance of social support perceived (Cronbach alpha: 0.923).

Post traumatic stress disorder test (PTSD)

The number of items in the original questionnaire had to be reduced in order to accommodate the study setting to avoid the exhaustion of our patients. To cover possible symptoms of PTSD, we selected 7 items. A summarized score was calculated. This tool cannot be used to diagnose PTSD or its severity, but it does identify the possible presence of it (Cronbach-alpha 0.807).

Statistical analyses

Statistical analyses were performed using the SPSS 25.0 software.To analyze and describe the associations between our variables we performed Pearson and Spearman correlations, Welch *t*-test, Mann-Whitney *U* test, Independent Samples *t* Test, and Chi-squared test. We intended to depict the predictability of the number of long-COVID symptoms. For this purpose we used Poisson regression as the most fitting method to our dependent variable. Based on biological plausibility and literature review we considered to following variables in our models that age, gender, family status, being an athlete or non-athlete, number of symptoms during the acute infection, affective factors (depression, anxiety, mental disorder, PTSD, social support, life satisfaction, COVID related traumatic event), and clinical factors (ferritin, CRP, haemoglobin, HDL, LDL-C, BMI index) effect on the number of long-COVID symptoms. *P* value of <0.05 was considered statistically significant in the performed tests.

RESULTS

Demographic and psychological baseline data

A total of 166 patients were enrolled in this study, including 119 sedentary/non-athletes and 47 athletes. Overall, 72 men and 94 women were enrolled. The mean age was 39 ± 14 years and the mean follow-up time was 25 ± 18 weeks after the diagnosis. Most of them lived in a relationship ($N = 111$), and part of the sample were regarded as single (widow, divorced, or not married so far ($N = 54$), while one person refused to answer this question. The majority of individuals in the sample indicated the presence of 2.5 ± 1.98 long-COVID symptoms. For further descriptive data and characteristics of the sample see Table 1.

The overall prevalence of depressive symptoms was high; 73.5% of patients reported symptoms consistent with at least mild depressive state. Anxiety was less common, 12% of patients reported moderate or more severe symptoms of anxiety. More than half of the subjects indicated symptoms suggesting PTSD (54.2%). The patients were mainly satisfied with their lives ($M = 7.73 \pm 1.792$) and they mostly had someone in their lives to rely on based on the social support scores ($M = 55.09 \pm 7.279$). See details in Table 1.

Pre-existing mental health problems

Pre-existing affective or anxiety problems were associated with a higher reported long-COVID symptom count (Table 2). Furthermore, we found significant correlation between pre-existing

Table 1. Demographic, affective and clinical characteristic of the sample and comparison of sample's subjects

Demographic				
	N	%	Skewness	Kurtosis
Sex				
Men	72	43.4		
Women	94	56.6		
Athlete				
Athletes	119	28.3		
Non-athletes	47	71.7		
	Mean	*SD*		
Age	39.06	14.49	0.74	−0.15
Marital status				
	N	%		
Married/In relationship	111	66.9		
Divorced/Single/Widowed	54	32.5		
Affective				
	Mean	*SD*		
Depression	12.14	4.09	0.62	1.16
Anxiety	9.79	11.03	1.43	1.88
Life satisfaction	7.73	1.79	−0.87	0.58
Social support	55.09	7.27	−2.07	5.20
PTSD	2.85	3.55	1.45	2.16
Clinical				
	Mean	*SD*		
Long-COVID symptom count	2.5	1.98	0.33	−0.76
CRP (mg L^{-1})	2.41	3.06	2.96	10.97
HGB (g L^{-1})	143.6	13.37	−0.43	0.29
LDL-C (mmol L^{-1})	3.14	0.80	0.19	−0.56

(continued)

Table 1. Continued

Clinical

	N	%
Hypertension	33	19.9
COPD/asthma	11	6.6

Abbreviations: PTSD – post-traumatic stress disorder, CRP - C Reactive Protein, LDL-C - LDL cholesterol, HGB – haemoglobin

Comparison of sample's subjects

	Women (M ± SD)	Men (M ± SD)	Effect size (d/r; v/c)	Athlete (M ± SD)	Non-Athlete (M ± SD)	Effect size (d/r; v/c)
Age	42.2 ± 14.4	34.8 ± 13.5	**d=0.52***/r=0.28*****	26.47 ± 6.1	44.04 ± 13.8	**d=1.44***/r=0.60*****
Depression	12.7 ± 4.4	11.3 ± 3.4	**d=0.34*/r=0.37*****	9.89 ± 1.6	13.03 ± 4.4	**d=0.81***/r=0.45*****
Anxiety	12.6 ± 11.6	5.9 ± 8.8	**d=0.63***/r=0.24*****	2.4 ± 6.6	12.7 ± 11.08	**d=1.02***/r=0.59*****
Life satisfaction	7.3 ± 1.8	8.2 ± 1.5	**d=0.52***/r=0.25*****	8.6 ± 1.9	7.37 ± 1.06	**d=0.72***/r=0.30*****
Social support	54.3 ± 7.2	56.07 ± 7.2	d=0.23/r=0.13	58.9 ± 2.2	53.5 ± 8.02	**d=0.78***/r=0.38*****
PTSD	3.9 ± 4	1.5 ± 2.2	**d=0.71***/r=0.34*****	0.7 ± 1.5	3.7 ± 3.7	**d=0.92***/r=0.69*****
CRP	2.9 ± 3.2	1.7 ± 2.6	**d=0.38*/r=0.25****	1.4 ± 1.4	2.8 ± 3.4	**d=0.44*** r=0.19****
HGB	135.1 ± 10.2	154.8 ± 7.4	**d=2.16*** r=0.72*****	149.5 ± 11.5	141.2 ± 13.3	**d=0.63***/r=0.27*****
LDL-C	3.1 ± 0.7	3.1 ± 0.8	d=0.01/r=0.02	2.7 ± 0.7	3.29 ± 0.7	**d=0.67*** r=0.28*****
Long-COVID symptom count	3.2 ± 1.9	1.6 ± 1.6	**d=0.86***/r=0.39*****	0.2 ± 0.6	3.2 ± 1.6	**d=2.01***/r=0.69*****
Hypertension	21	12	v=0.07/c=0.07	2	31	**v=0.24/c=0.23****
No Hypertension	73	60		45	88	
COPD/Asthma	8	3	v=0.87/c=0.86	0	11	**v=0.16/c=1.6***
No COPD/Asthma	86	69		47	108	

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, Chi-squared test Cramer's V (*v*) and Contingency Coefficients (c) and independent samples *t*-test (d) and Mann Whitney *U* test (r).

Abbreviations: PTSD – post-traumatic stress disorder, CRP – C Reactive Protein (mg L^{-1}), LDL-C – LDL cholesterol (mmol L^{-1}), HGB – haemoglobin (g L^{-1}).

Table 2. Associations between clinical factors and affective psychological constructs

	Depression r/rho	PTSD r/rho	Anxiety r/rho	Life satisfaction r/rho	Social support r/rho
CRP (mg L^{-1})	−0.03/−0.01	0.12/0.12	0.08/0.13	−0.02/−0.04	−0.009/0.02
HGB (g L^{-1})	**−0.15*****/−0.21****	**−0.29******/−0.31****	**−0.21******/−0.27****	**0.18*****/0.23****	**0.19*****/0.21****
LDL-C (mmol L^{-1})	**0.12/0.16***	**0.14/0.15**	**0.11/0.17***	−0.11/−0.09	−0.08/−0.14
	d/r	**d/r**	**d/r**	**d/r**	**d/r**
Hypertension	0.24/**0.17***	−0.46/**0.18***	**0.39*****/0.25*****	**0.41*****/0.19***	**0.54******/0.27*****
COPD/asthma	**0.78*****/0.17***	0.77/0.08	**0.87******/0.22****	1.06/**0.81***	0.69/0.08
Previous mental health problems	**0.87*******/0.37*****	**0.87*******/0.33*****	**1.17*******/0.40*****		

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, Pearson (r) Spearman (rho) and independent samples *t*-test (d) and Mann Whitney *U* test (r).
Abbreviations: PTSD – post-traumatic stress disorder, CRP – C Reactive Protein, LDL-C – LDL cholesterol, HGB – haemoglobin.

mental health problems and the investigated psychological constructs. Individuals with these conditions reported higher level of anxiety, depression and PTSD than patients without any formerly existing mood or anxiety problems at the time of examination.

Number of long-COVID symptoms

The number of long-COVID symptoms were reported on a scale between 0 and 9 (n=156). The minimum was 0 while the maximum was 8 reported symptoms. Neither the skewness nor kurtosis exceed 1, therefore the normality was not violated. It was observed that the symptom count of the acute infection phase was positively correlated with the number of symptoms in long-COVID. The athletes reported fewer symptoms than the non-athletes. Regarding sex differences, women indicated more symptoms than men. We studied the associations of long-COVID symptom count with affective (mental) and clinical (blood test, comorbidities) perspectives.

Associations between the long-COVID symptom count and affective factors

With **depression,** we found a moderate, positive association; a higher level of depression attends with more long-COVID symptoms. The result was similar in respect of **anxiety**. A moderate, positive association between **PTSD** and the number of long-COVID symptoms was detected. **Life satisfaction** and social support were found to be moderating factors. Based on our findings, the higher the level of life satisfaction and the percieved social support, the lower the number of symptoms (mild and moderate negative correlation).

Associations between the number of the long-COVID symptoms and clinical factors

Our research revealed two significant associations between the results of the blood tests and the number of long-COVID symptoms. Higher level of **HGB** showed negative and mild relation to

Table 3. Associations of long-Covid with affective and clinical factors

	Effect size (r/rho; d/r)
Demographic	
Age	**0.34******/0.44**
Being an athlete	**2.01*******/0.69*****
Sex	**0.86*******/0.39*****
Affective	
Depression	**0.57******/0.64****
Anxiety	**0.58******/0.66****
Life satisfaction	**−0.49******/−0.39****
Social support	**−0.35******/−0.39****
PTSD	**0.47******/0.49****
Clinical	
CRP (mg L^{-1})	−0.02/0.04
HGB (g L^{-1})	**−0.28******/−0.30****
LDL-C (mmol L^{-1})	**0.20*****/0.21****
No. of symptoms in acute phase	**0.57******/0.59****
Hypertension	**0.44*****/0.19***
COPD/asthma	**0.77*****/0.17***

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, Pearson (r) Spearman (rho) and independent samples *t*-test (d) and Mann Whitney *U* test (r).
Abbreviations: PTSD – post-traumatic stress disorder, CRP – C Reactive Protein, LDL-C – LDL cholesterol, HGB – haemoglobin.

the number of symptoms, while the level of **LDL-C** a mild, positive association. Patients with **hypertension** indicated more symptoms than people with normal blood pressure. Patients with **COPD or asthma** reported more long-COVID symptoms than individuals without this condition (Table 3).

Clinical factors and affective psychological constructs

Our research suggests that higher HGB levels are associated with higher life satisfaction and perceived social support, while lower levels are associated with higher depression and anxiety values. **LDL-C** shows a positive connection with affective factors such as anxiety, and depression. We found significant relationships between existing **COPD/asthma**, **hypertension** and affective factors (depression, anxiety, social support, life satisfaction, PTSD). See the detailed statistical data in Table 3.

Possible predictors of the number of the long-COVID symptoms

In this study we sought to identify those variables that might predict or contribute to the number of long-COVID symptoms. First, based on previous research results and scientific considerations, we chose a series of variables that might affect the number of experienced symptoms (age, gender, being an active sports player, number of acute infection, affective psychological variables, social support, and clinical variables). In terms of our Poisson regression, 4 variables were included in our model as possible predictors of the number of long-COVID symptoms (Table 4). According

Table 4. Correlational matrix

	Life satisfaction		Social support		PTSD		No. of long-COVID sympts.		No. of sympts. in acute phase		CRP		HGB		LDL-C		Depression		Anxiety	
	r	rho	r	rho	r	rho	r	rho	r	rho	r	rho	r	rho	r	rho	r	rho	r	rho
Age	**−0.20****	**−0.21****	**−0.23****	**−0.26****	**0.32****	**0.39****	**0.34****	**0.44****	**0.20****	**0.26****	**0.18***	**0.25****	**−0.18***	**−0.20****	**0.35****	**0.42****	0.11	**0.27****	**0.27****	**0.41****
Life satisfaction			**0.57****	**0.57****	**−0.38****	**−0.35****	**−0.49****	**−0.49****	**−0.25****	**−0.25****	−0.02	−0.04	**0.18***	**0.23****	−0.11	−0.09	**−0.60****	**−0.66****	**−0.43****	**−0.44****
Social support					**−0.34****	**−0.37****	**−0.35****	**−0.39****	**−0.22****	**−0.31****	−0.009	0.02	**0.19***	**0.21****	−0.08	−0.14	**−0.49****	**−0.56****	**−0.41****	**−0.45****
PTSD							**0.47****	**0.49****	**0.39****	**0.41****	0.12	0.12	**−0.29****	**−0.31****	0.14	0.15	**0.59****	**0.57****	**0.71****	**0.65****
No. of long-COVID sympts.									**0.57****	**0.59****	−0.02	0.04	**−0.28****	**−0.30****	**0.20***	**0.21****	**0.57****	**0.64****	**0.58****	**0.66****
No. of sympts. in acute phase											0.08	0.07	**−0.19***	**−0.22****	**0.18***	**0.18***	**0.36****	**0.43****	**0.48****	**0.56****
CRP													−0.13	**−0.16***	0.001	**0.17***	−0.03	−0.01	0.08	0.13
HGB															0.09	0.09	**−0.15***	**−0.21****	**−0.21****	**−0.27****
LDL-C																	0.12	**0.16***	0.11	**0.17***
Depression																			**0.57****	**0.61****
Anxiety																				

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Abbreviations: PTSD – post-traumatic stress disorder, CRP – C Reactive Protein (mg L^{-1}), LDL-C – LDL cholesterol (mmol L^{-1}), HGB – haemoglobin (g L^{-1}).

Table 5. Poisson regression models of the number of long-COVID symptoms

Parameters	B	Exp(B)	Wald Chi-Square	SIG
Age	0.01	1.01	11.29	0.001
Life satisfaction	−0.06	0.93	4.06	0.044
Number of sympts. during acute infect.	0.15	1.17	34.45	0.000
Depression	0.04	1.04	10.47	0.001
Omnibus Test				
Likelihood-Ratio Chi-Square		df		SIG
129.88		4		0.000
Goodness of Fit				
	Value		df	Value/df
Deviance	170.79		145	1.17
Scaled Deviance	170.79		145	
Pearson Chi-Square	141.67		145	0.97
Scaled Pearson Chi-Square	141.67		145	

to the exponentiation of the B coefficient, number of symptoms during acute infection, life satisfaction, depression, and age found to be the strongest factors that may play a role in mid and long-term long-COVID symptom development. Based on the fit indicators, the model fits well, the values of the indicator are close to 1. Interpreting the exponentiation of the B coefficient, our results point out that if the symptom count of the acute infection increases by one, then it causes a 17.2% increase in the number of long-COVID symptoms (Table 5).

DISCUSSION

Our study's main strength is that it focuses on a scarcely studied group and besides this population's prime affective characteristics, it points out more complex results by involving clinical factors. This approach allows a multidirectional understanding of the subject. The significance of our results is shown by the fact that patients with mild symptoms without hospitalisation account for the majority of COVID patients. Our aim was to examine the affective and physiological relationships among symptoms in non-hospitalized long-COVID patients.

History of mental health problems like depression or anxiety are associated with the severity of mental health symptoms. Taquet et al. [5] found that psychiatric conditions have a bidirectional association with diagnosis of COVID-19. Current mental health conditions might increase the probability of the COVID-19 infection independently of the physical health risk factors. Furthermore, the diagnosis of COVID-19 is associated with the emergence of a first psychiatric diagnosis [5]. Diagnosis of depression or anxiety and female sex are risk factors concerning COVID-19 related fatigue [27]. Indeed, women experience more severe and persistent mental health symptoms after COVID-19 infection and they are at higher risk of long-COVID than men [28]. According to the illness and symptom representation models [10, 29] people diagnosed with an illness build a peculiar pattern or interpretation framework of their diseases based on

their knowledge, and their previous experience. Final evaluation before constructing this representation model is made based on a cognitive process which in the state of depression and anxiety might be strongly biased. The reason for this is among other, that hypervigilance is a characteristic of the elevated anxiety [9]. As a consequence of hypervigilance anxious people strongly focus on their somatic signs. Additionally, individuals with depressive affect are more self-focused and tend to ruminate which enhance the attention of the minor somatic changes [9]. According to the study of Howren et al. [9] elevated anxiety predisposes the report of more concurrent physical symptoms while depressive affect is related to the account of more physical symptom frequency from previous weeks. In our study, we found that those individuals who reported pre-existing mental disorders had more severe concurrent depression and anxiety than people without these conditions and they also reported more long-COVID symptoms.

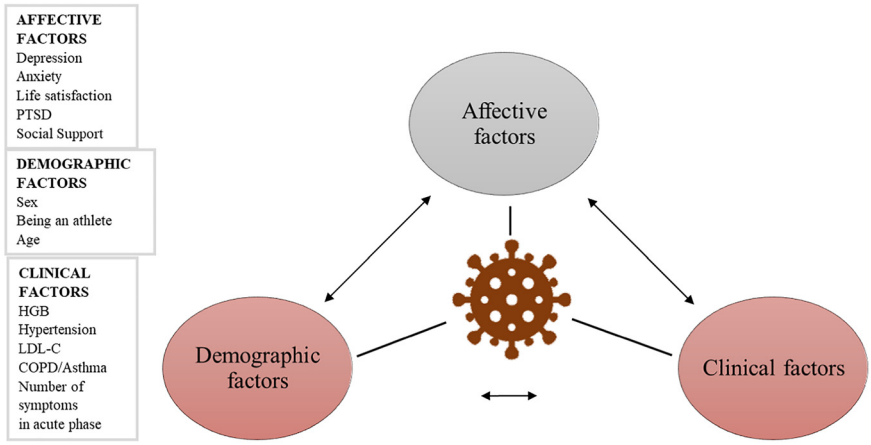
We found a positive correlation between the **number of long-COVID symptoms** and the number of symptoms indicating depression, anxiety and PTSD, this means that individuals with higher levels of depressive complaints and anxiety are experiencing more long-COVID related symptoms too. On the other hand social support and life satisfaction are found to be protective factors against long-COVID symptom burden. Regarding sex differences, women indicated more symptoms than men.

These results are consistent with previous research on depression, PTSD, and anxiety in COVID-19 infection, however, to the best of our knowledge, no data were available so far regarding the correlations of the number of the long-COVID symptoms and affective psychological constructs on non-hospitalized patients. The COVID-19 patients are at higher risk of **anxiety and depression** than the general population [30, 31]. The prevalence of depression in this population is approximately 42% [30, 31]. Regarding anxiety, the prevalence is similarly high, approximately 40% [30, 31]. The high level of anxiety and depression (37.5%) was also recorded in a study involving hospitalized post-COVID patients from 30 to 180 days after the diagnosis.

In our study, we found that patients with more long-COVID symptoms had lower **HGB** levels, and higher LDL-C levels compared to patients with fewer symptoms. These associations and mechanisms are not clear yet but concerning the HGB, changes in iron metabolism or the reduced response of cerebral blood vessels may contribute to mood disorders [32, 33]. Van Reedt Dortland found that persistent dyslipidemia and atypical depression are associated, which might be explained by the LDL-C increasing effect of the symptoms of depression, such as increased appetite and fatigue and decreased physical activity [34]. There is evidence that certain pre-existing medical conditions like COPD or asthma are risk factors of long-COVID [35]. In our study patients with **hypertension** and **COPD** reported more symptoms than people with no pre-existing medical condition.

Former studies have already pointed out the associations of depression and anxiety with blood test parameters; we have also checked them to investigate the multidirectional nature of this topic [11, 12]. Our findings strengthen the earlier results as follows: level of HGB is in a mild negative association with depression and anxiety, but positive correlation with life satisfaction and perceived social support. A positive relationship exists between LDL-C and depression, PTSD and anxiety. We found a positive correlation between COPD/asthma and hypertension and affective factors. People with these conditions reported a higher level of anxiety, while depression is positively correlated with COPD/asthma.

Galal et al. [36] investigated former COVID-19 patients to evaluate the frequency and determinants of post-COVID 19 symptoms. They found that the acute phase symptom severity and



Abbreviations: PTSD – post-traumatic stress disorder, CRP - C Reactive Protein, LDL-C - LDL cholesterol, HGB – haemoglobin

Fig. 1. Multifactorial nature of the development of the number of long-COVID symptoms

any comorbid disease, including worsened mental health increase the risk of the manifestation of post-COVID symptoms. Another study also confirmed that female sex, depression, and anxiety symptoms increase the risk of the onset of persistent post-COVID symptoms [37]. Our findings partially confirm these results, as in our regression model acute symptomatology and depression might predict the number of long-covid symptoms. In this case, the number of symptoms during acute infection, depression, age, and life satisfaction composed of our model. Out of our variables these seems to be the strongest factors that contribute to having several symptoms experienced in the mid and long-term but of course, not to the emergence of the condition itself. Figure 1 gives insight into the multidimensional factors we found related to the long-COVID symptom count.

CONCLUSION

Our study suggests bi-directional interconnection between clinical and psychological factors. Additional contributing factors are presented in a regression model, in which the number of symptoms in the acute phase, age, depression and life satisfaction also contribute to the amount of long-COVID symptoms. Moreover, certain laboratory parameters may have an additional role in predicting higher long-COVID symptom burden and are associated with anxiety and depression.

LIMITATIONS

Our sample was relatively small, limiting our possibilities of detecting even small differences. Further, the nature of the sampling procedure might limit the generalizability of our findings. Unmeasured confounding factors may also modify the applicability of our data. Regarding the

selection, two groups of participants were involved in the study. Also, this is a single-center study.

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REFERENCES

1. World Health Organization. WHO COVID-19 dashboard Geneva: World Health Organization; 2020 [cited 2021 Dec 21]. Available from: https://covid19.who.int/.
2. Aiyegbusi OL, Hughes SE, Turner G, Rivera SC, McMullan C, Chandan JS, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med 2021; 114(9): 428–42. https://doi.org/10.1177/01410768211032850.
3. Poyraz B, Poyraz CA, Olgun Y, Gürel Ö, Alkan S, Özdemir YE, et al. Psychiatric morbidity and protracted symptoms after COVID-19. Psychiatry Res 2021; 295: 113604. https://doi.org/10.1016/j.psychres.2020.113604.
4. Shanbehzadeh S, Tavahomi M, Zanjari N, Ebrahimi-Takamjani I, Amiri-Arimi S. Physical and mental health complications post-COVID-19: scoping review. J Psychosom Res 2021; 147: 110525. https://doi.org/10.1016/j.jpsychores.2021.110525.
5. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021; 8(2): 130–40. https://doi.org/10.1016/s2215-0366(20)30462-4.
6. Grey I, Arora T, Thomas J, Saneh A, Tohme P, Abi-Habib R. The role of perceived social support on depression and sleep during the COVID-19 pandemic. Psychiatry Res 2020; 293: 113452. https://doi.org/10.1016/j.psychres.2020.113452.
7. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the brief illness perception questionnaire. Psychol Health 2015; 30(11): 1361–85. https://doi.org/10.1080/08870446.2015.1070851.
8. Sawyer AT, Harris SL, Koenig HG. Illness perception and high readmission health outcomes. Health Psychol Open 2019; 6(1): 2055102919844504. https://doi.org/10.1177/2055102919844504.
9. Howren MB, Suls J. The symptom perception hypothesis revised: depression and anxiety play different roles in concurrent and retrospective physical symptom reporting. J Pers Soc Psychol 2011; 100(1): 182–95. https://doi.org/10.1037/a0021715.
10. Leventhal H, Leventhal EA, Cameron L. Representations, procedures, and affect in illness self-regulation: a perceptual-cognitive model. In: Baum A, Revenson TA, Singer JE, editors. Handbook of health psychology. Mahwah: Lawrence Erlbaum Associates Inc.; 2001. pp. 19–47.

11. Köhler-Forsberg O, Buttenschøn HN, Tansey KE, Maier W, Hauser J, Dernovsek MZ, et al. Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. Brain Behav Immun 2017; 62: 344–50. https://doi.org/10.1016/j.bbi.2017.02.020.
12. Wagner CJ, Musenbichler C, Böhm L, Färber K, Fischer AI, von Nippold F, et al. LDL cholesterol relates to depression, its severity, and the prospective course. Prog Neuropsychopharmacol Biol Psychiatry 2019; 92: 405–11. https://doi.org/10.1016/j.pnpbp.2019.01.010.
13. Vahdat Shariatpanaahi M, Vahdat Shariatpanaahi Z, Moshtaaghi M, Shahbaazi SH, Abadi A. The relationship between depression and serum ferritin level. Eur J Clin Nutr 2007; 61(4): 532–5. https://doi.org/10.1038/sj.ejcn.1602542.
14. Skarstein J, Bjelland I, Dahl AA, Laading J, Fosså SD. Is there an association between haemoglobin, depression, and anxiety in cancer patients? J Psychosom Res 2005; 58(6): 477–83. https://doi.org/10.1016/j.jpsychores.2005.02.003.
15. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. J Clin Lab Anal 2020; 34(10): e23618. https://doi.org/10.1002/jcla.23618.
16. Feingold KR. The bidirectional link between HDL and COVID-19 infections. J Lipid Res 2021; 62: 100067. https://doi.org/10.1016/j.jlr.2021.100067.
17. Merzon E, Green I, Shpigelman M, Vinker S, Raz I, Golan-Cohen A, et al. Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. Diabetes Metab Res Rev 2021; 37(5): e3398. https://doi.org/10.1002/dmrr.3398.
18. Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. C-reactive protein level may predict the risk of COVID-19 aggravation. Open Forum Infect Dis 2020; 7(5): ofaa153. https://doi.org/10.1093/ofid/ofaa153.
19. National Institute for health and Care excellence: clinical guidelines. COVID-19 rapid guideline: managing the long-term effects of COVID-19. London: National Institute for Health and Care Excellence (NICE); 2020.
20. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of sex, age, and comorbidities with mortality in COVID-19 patients: a systematic review and meta-analysis. Intervirology 2021; 64(1): 36–47. https://doi.org/10.1159/000512592.
21. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med 2021; 27(4): 601–15. https://doi.org/10.1038/s41591-021-01283-z.
22. Tamasi J, Kalabay L. Poszt-COVID–19-szindrómás esetek kialakulásának követése [Monitoring the development of post-COVID–19 syndrome]. Orv Hetil 2022; 163(9): 335–42. https://doi.org/10.1556/650.2022.32432.
23. Rózsa S, Szádóczky E, Füredi J. A Beck depresszió kérdőív rövidített változatának jellemzői hazai mintán [Psychometric properties of the Hungarian version of the shortened Beck Depression Inventory]. Psychiatria Hungarica 2001; 16(4): 384–402.
24. Perczel-Forintos D, Ajtay G, Barna C, Kiss Z, Komlósi S. Beck szorongás leltár. In: Perczel-Forintos D, Ajtay G, Barna C, Kiss Z, Komlósi S, editors. Kérdőívek, becslőskálák a klinikai pszichológiában. 4th rev. and expand. ed. Budapest: Semmelweis Kiadó; 2018. pp. 13–4.
25. Cheung F, Lucas RE. Assessing the validity of single-item life satisfaction measures: results from three large samples. Qual Life Res 2014; 23(10): 2809–18. https://doi.org/10.1007/s11136-014-0726-4.
26. Papp-Zipernovszky O, Kékesi MZ, Jámbori S. A Multidimenzionális Észlelt Társas Támogatás Kérdőív magyar nyelvű validálása [Validation of the Hungarian version of multidimensional scale of perceived social support]. Mentálhigiéné és Pszichoszomatika 2017; 18(3): 230–62. https://doi.org/10.1556/0406.18.2017.011.

27. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One 2020; 15(11): e0240784. https://doi.org/10.1371/journal.pone.0240784.
28. Bucciarelli V, Nasi M, Bianco F, Seferovic J, Ivkovic V, Gallina S, et al. Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: gender makes a difference. Trends Cardiovasc Med 2022; 32(1): 12–7. https://doi.org/10.1016/j.tcm.2021.09.009.
29. Costa PT, Jr., McCrae RR. Neuroticism, somatic complaints, and disease: is the bark worse than the bite? J Pers 1987; 55(2): 299–316. https://doi.org/10.1111/j.1467-6494.1987.tb00438.x.
30. Krishnamoorthy Y, Nagarajan R, Saya GK, Menon V. Prevalence of psychological morbidities among general population, healthcare workers and COVID-19 patients amidst the COVID-19 pandemic: a systematic review and meta-analysis. Psychiatry Res 2020; 293: 113382. https://doi.org/10.1016/j.psychres.2020.113382.
31. Wu T, Jia X, Shi H, Niu J, Yin X, Xie J, et al. Prevalence of mental health problems during the COVID-19 pandemic: a systematic review and meta-analysis. J Affect Disord 2021; 281: 91–8. https://doi.org/10.1016/j.jad.2020.11.117.
32. Matsuo K, Kato N, Kato T. Decreased cerebral haemodynamic response to cognitive and physiological tasks in mood disorders as shown by near-infrared spectroscopy. Psychol Med 2002; 32(6): 1029–37. https://doi.org/10.1017/s0033291702005974.
33. Noorazar Sg, Ranjbar F, Nemati N, Yasamineh N, Kalejahi P. Relationship between severity of depression symptoms and iron deficiency anemia in women with major depressive disorder. J Anal Res Clin Med 2015; 3(4): 219–24. https://doi.org/10.15171/jarcm.2015.034.
34. van Reedt Dortland AK, Giltay EJ, van Veen T, van Pelt J, Zitman FG, Penninx BW. Associations between serum lipids and major depressive disorder: results from The Netherlands Study of Depression and Anxiety (NESDA). J Clin Psychiatry 2010; 71(6): 729–36. https://doi.org/10.4088/JCP.08m04865blu.
35. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med 2021; 27(4): 626–31. https://doi.org/10.1038/s41591-021-01292-y.
36. Galal I, Hussein A, Amin MT, Saad MM, Zayan HEE, Abdelsayed MZ, et al. Determinants of persistent post-COVID-19 symptoms: value of a novel COVID-19 symptom score. Egypt J Bronchol 2021; 15(1): 10. https://doi.org/10.1186/s43168-020-00049-4.
37. Knight DRT, Munipalli B, Logvinov, II, Halkar MG, Mitri G, Dabrh AMA, et al. Perception, prevalence, and prediction of severe infection and post-acute sequelae of COVID-19. Am J Med Sci 2022; 363(4): 295–304. https://doi.org/10.1016/j.amjms.2022.01.002.