Do Anxiety and Depression Predict Persistent Physical Symptoms After a Severe COVID-19 Episode? A Prospective Study

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Background: Persistent physical symptoms are common after a coronavirus disease 2019 (COVID-19) episode, but their pathophysiological mechanisms remain poorly understood. In this study, we aimed to explore the association between anxiety and depression at 1-month after acute infection and the presence of fatigue, dyspnea, and pain complaints at 3-month follow-up.

Methods: We conducted a prospective study in patients previously hospitalized for COVID-19 followed up for 3 months. The Hospital Anxiety and Depression Scale (HAD-S) was administered by physicians at 1-month follow-up, and the presence of fatigue, dyspnea, and pain complaints was assessed at both 1 month and 3 months. Multivariable logistic regressions explored the association between anxiety and depression subscores and the persistence of each of the physical symptom at 3 months.

Results: A total of 84 patients were included in this study (Median age: 60 years, interquartile range: 50.5–67.5 years, 23 women). We did not find any significant interaction between anxiety and the presence of fatigue, dyspnea, or pain complaints at 1 month in predicting the persistence of these symptoms at 3 months (all \( p > 0.36 \)). In contrast, depression significantly interacted with the presence of pain at 1 month in predicting the persistence of pain at 3 months (OR: 1.60, 95% CI: 1.02–2.51, \( p = 0.039 \)), with a similar trend for dyspnea (OR: 1.51, 95% CI: 0.99–2.28, \( p = 0.052 \)).
INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has widely spread worldwide (1). Approximately 20% of infected individuals develop severe illness, requiring hospitalization, but most experience mild symptoms, and did not beneﬁcate for a long-lasting follow-up (2). Among these patients, a substantial number still present clinical symptoms at a signiﬁcant distance from acute infection (3–6). A meta-analysis including 1,816 hospitalized patients found that fatigue, dyspnea, chest pain, and cough, were the most prevalent persistent symptoms in 52, 37, 16, and 14% of survivors between 3 weeks and 3 months after hospitalization, respectively (6). These persistent physical symptoms following COVID-19 are now referred to as “Long COVID,” or “Post-COVID syndrome.” However, it is noteworthy that they may not be speciﬁc to SARS-CoV-2 infection (7). Indeed, although the prevalence of these persistent symptoms is now better known, little is known about their pathophysiological mechanisms as well as the potential clinical predictive factors that could be used for prevention strategies. This question could therefore represent a major public health concern over the next few years, and supports the urgent need to understand the pathophysiological mechanisms and clinical predictors of these symptoms (8, 9).

Several hypotheses have been formulated to explain these persistent physical symptoms, such as the impact of direct effects of the virus, sequelae of neurological damage, persistent inﬂammatory syndrome, or involvement of cognitive mechanisms akin to those observed in functional somatic disorders (8). Severe acute respiratory syndrome coronavirus 2 infection produce inflammatory disturbing, up to a so-called “cytokine storm” (i.e., a systemic production of cytokines, chemokines, and inﬂammatory mediators) (10). This immune-inﬂammatory activation may induce thromboses and vascular damages, and disturb hypothalamo-pituitary-adrenal and neuroendocrine axes (11). In addition to these causes, psychiatric symptoms could be one of the keys in understanding these persistent physical symptoms (12, 13).

Psychiatric symptoms are frequently found after a coronavirus infection such as SARS-CoV-1 or MERS-CoV (14–16). Supporting these ﬁndings, current reports showed that SARS-CoV-2 infection is associated with a high prevalence of anxiety and depression afterwards (17–19). Persistent and disabling symptoms could induce depressive symptoms and anxiety (20–22) and persistent physical symptoms after COVID-19, including gastrointestinal and respiratory symptoms, are signiﬁcantly associated with a higher probability of developing psychiatric symptoms (19, 23, 24). Reciprocally, however, patients presenting with depression and anxiety also tend to have more somatic and pain complaints (25). Anxiety and depression have been identiﬁed as highly associated with persistent symptoms in several conditions (26), including fatigue after COVID-19 (27). Furthermore, among the most frequent persistent symptoms after COVID-19, many are either core diagnostic criteria for depressive or anxiety disorders (i.e., fatigue, sleep disorders, cognitive disturbances) or symptoms frequently associated with these disorders (e.g., dyspnea and panic disorder, pain and depressive disorders). For instance, a study from our group found that cognitive complaints at 1 month after follow-up were better explained by the levels of anxiety and depression than by objective neuropsychological functioning (28). The high prevalence of anxiety and depression symptoms after COVID-19 may thus partially account for some persistent symptoms. Nevertheless, this hypothesis may have been somewhat overlooked so far, despite clear clinical implications, as evidence-based treatments are available for both depression and anxiety.

In this preliminary study, we aimed to explore the association between anxiety and depression 1 month after hospitalization for acute SARS-CoV-2 infection and the presence of persistent physical symptoms (fatigue, dyspnea, and pain complaints) after 3 months. Specifically, we thought that persistent physical symptoms would particularly occur in patients presenting both a physical symptom and manifestations of anxiety and depression. First, the presence of both at 1 month could indicate that the persistent physical symptom is potentially a psychiatric symptom. Second, anxiety and depression may share some vulnerability factors with functional somatic symptoms (e.g., female gender, high level of neuroticism) and thus be associated with an increased risk of persistent physical symptoms after an acute COVID-19. In other words, we hypothesized that anxiety and depression at 1 month would predict persistent physical symptoms at 3 months for patients presenting these symptoms at 1 month.

MATERIALS AND METHODS

Population

The study is part of The French COVID cohort (NCT04262921) that was authorized by the French Ethics Committee (ID RCB:2020-A00256-33). All inpatients aged 18 or more who were hospitalized at European Hospital Georges Pompidou for a SARS-CoV-2 infection (according to WHO criteria) during the first wave of the COVID-19 pandemic, between March 17th and April 29th, 2020 were included. Participants underwent a
standardized physical evaluation by a senior physician at the
time of the inclusion (i.e., within the first 48 h of hospital
admission for COVID-19). Socio-demographic data as well as
clinical and biological data regarding the infection were recorded
at inclusion, using a standardized medical form. Clinical data
included admission in intensive care unit (ICU) as a proxy of
severity of the infection. Written informed consent was obtained
for all participants.

Patients who were discharged less than a month after the
hospitalization for COVID-19 were proposed a clinical follow-
up at 1 month, 3 months, and 6 months, either during a 1-
day outpatient clinical examination or by teleconsultation. The
present study is based on data collected during 1-day outpatient
clinical examinations at 1 month and 3 months.

**Clinical Assessment**

To assess anxiety and depression symptoms, the Hospital Anxiety
and Depression Scale (HAD-S) was filled at 1-month follow-up. The
HAD-S encompasses 14 items coded 0–3 and two subscales
(HADS-A: seven items measuring symptoms of anxiety; HADS-
D: seven items measuring symptoms of depression). Several
studies have shown valid psychometric properties for HAD-S
subscales in the general population (29), in patients suffering
from various pathologies (30), for older patients aged 65–80
years (31), and in different countries (32). In the present study,
the Cronbach's alpha coefficient for the global score, the anxiety
subscore and the depression subscore was 0.86, 0.84, and 0.72,
respectively, suggesting satisfactory internal consistency.

Patients also underwent a clinical examination at 1- and 3-
month follow-up that included a general physical examination
with systematic assessment of the following residual symptoms:
agueusia, anosmia, cough, dyspnea, myalgia, arthralgia, fatigue,
headache, rhinorrhea, diarrhea, nausea. Here, we focused on
fatigue, dyspnea, and pain complaints (defined as presenting with
arthralgia, myalgia, or headache) that were self-reported. Clinical
examinations were performed by a team of physicians working in
the same hospital, but each patient was not necessarily examined
by the same clinician.

The presence of a restrictive ventilatory defect, defined as
having a total lung capacity <80% at spirometry test at 1-month
follow-up was also recorded, as an alternative proxy of severity of
the infection. Patients also had biological investigations including
measure of the blood level of C-reactive protein (CRP), an
inflammatory marker, at 1-month.

Between March 17th and April 29th, 2020, 354 patients
hospitalized at HEGP were included in the French COVID
cohort. Among these patients, 29 were lost at follow-up because of
inter-hospital transfer, 78 died and 2 withdrew their consent.
Among the 245 patients eligible for the clinical follow-up, 7 died
during the follow-up, 22 withdrew their consent, and 6 were not
reachable. Among the 210 remaining patients who underwent
the follow-up, 132 attended the 1-day follow-up examination at 1 month, including 109 who also attended the 1-day follow-
up examination at 3 months. Among these 109 patients, 84 had
HAD-S data at 1-month follow-up. **Figure 1** presents the flow of
the study participants.

**Statistical Analysis**

Descriptive analyses were performed for the categorical and
continuous variables of interest.

For each physical symptom considered (i.e., fatigue, dyspnea,
and pain complaints), two different binary logistic regression
models were built for the two dimensions of the HAD-S
(Anxiety and Depression), as some symptoms may be particularly
in link with one of those dimension (e.g., fatigue or pain
complaints with depression). The outcome was the presence
of the physical symptom at 3 months and the predictive
variables were its presence at 1 month and one of the HAD-
S subscores. Furthermore, to test our hypothesis, every binary
logistic regression models included an interaction term between
the presence of the physical symptom at 1 month and the HAD-
S subscore. All models were also adjusted for age, sex, and
admission in ICU (as a clinical marker of the initial severity of
the infection).

We ran sensitivity analyses to test the robustness of our results:
admission in ICU was successively replaced with the presence
of a restrictive ventilatory defect at 1 month, the blood level
of CRP at 1 month (log-transformed), and the presence of a
medical comorbidity (i.e., diabetes or high blood pressure) at 1
month. The significance threshold was \( p < 0.05 \). All analyses were
performed using Stata 15.0 (StataCorp, College Station, TX).
RESULTS

The characteristics of the 84 participants [23 women, median age: 60 (interquartile range (iQR): 50.5–67.5] are displayed in Table 1.

Table 2 displays the results of the six different multivariable logistic regressions models searching for an interaction between each of the physical symptoms considered (fatigue, dyspnea, and pain complaints) and each of the HADS subscore (anxiety and depression) at 1 month in predicting the persistence of the symptom at 3 months.

For anxiety, we did not find any significant interaction between anxiety and fatigue, dyspnea, or pain complaints at 1 month in predicting the persistence of any of these symptoms at 3 months. For depression, we found a significant interaction with the presence of pain at 1 month in predicting the persistence of pain at 3 months, with a similar, yet not significant trend for dyspnea (Table 2). Concerning the other variables included in the regression models, none of them were significantly associated with the presence of any symptom at 3 months.

Replacing “admission in ICU” with another variable measuring the severity of the infection or possible sequelae (i.e., level of CRP at 1-month follow-up or having a restrictive ventilatory defect at 1-month follow-up), or comorbid conditions associated with more severe infection (i.e., diabetes or high blood pressure) did not change the observed associations or size effects. The depression by pain complaints interaction remained significant [adjusted OR [confidence interval (CI)]: 1.78 [1.05–3.02], 1.61 [1.01–2.55], 1.60 [1.02–2.51], and 1.68 [1.04–2.72], when adjusting for restrictive ventilatory defect, CRP level, comorbid diabetes, and comorbid high blood pressure, respectively], while the observed trend for the depression by dyspnea interaction even reached statistical significance for the sensitivity analysis adjusted for restrictive ventilatory defect, comorbid diabetes, and comorbid high blood pressure (adjusted OR [95% CI]: 1.57 [1.01–2.44], 1.57 [1.02–2.41], and 1.51 [1.01–2.25], respectively].

DISCUSSION

In our study, we explored the associations between anxiety and depression at 1 month after hospitalization for COVID-19 and persistent physical symptoms at 3 months. Although we did not find any evidence that anxiety may predict the persistence of fatigue, dyspnea, and pain complaints, there was a significant interaction between depression and pain complaints in predicting the persistence of those complaints, and a similar trend between depression and dyspnea.
We specifically found that the interaction between presenting at 1 month with pain complaints and greater HAD-S depression subscore was significantly associated with persisting pain complaints at 3 months. This latter result, indicating that patients with both a pain complaint and greater depressive symptoms at 1 month were more likely to present with persisting pain complaints at 3 months, is in line with previous and well-known findings, linking depression with more frequent pain complaints on one hand (12) and the persistence of physical symptoms after an acute infectious episode on the other hand (26). Although the lack of interaction with fatigue is at odd with recent findings suggesting that a history of depression may predict persistent fatigue in patients with COVID-19 (27), these discrepancies may be explained by the fact that current depression symptoms and history of depression are two different measures. In addition, it is noteworthy that our analyzes focused on the persistence of physical symptoms at 3 months rather than on the presence of these symptoms at 1 month. Interestingly, depression alone or pain alone at 1 month did not predict pain at 3 months. First, depression is frequently, yet not systematically associated with pain. Therefore, depression without pain at 1 month may indicate that there is no link between these two dimensions in a given patient, thus explaining why depression alone at month may not predict pain at 3 months. Second, pain without depression at 1 month may be associated with a more favorable course, for instance because of more adaptive health behaviors (e.g., higher levels of physical activity), than pain with depression, explaining why pain alone at month may not predict pain at 3 months.

Furthermore, our results approached statistical significance regarding dyspnea, in line with previous findings (13). Given the limited statistical power, our results are intriguing and should be the subject of further investigations. Several hypotheses could be explored regarding mechanisms accounting for the association between persistent painful complaints and depression after a severe COVID-19 episode. In particular, these persistent physical symptoms might be experienced more intensely by depressed patients, or these dimensions might involve shared factors such as a high level of neuroticism (i.e., tendency to experience negative emotions such as anger, fear, or sadness with limited tolerance for aversive stimuli) (33, 34). Noteworthy, our cohort may not be representative of the patients diagnosed with “long COVID” who are mostly young women with mild initial infection, so our results may not be generalized to these patients. Further studies should explore the role of these psychological dimensions regarding persistent physical symptoms after mild and severe COVID-19 episodes.

Regarding anxiety, our results do not suggest that general anxiety is predictive of persistent physical symptoms in COVID-19 survivors. It could be argued that having been included in a research cohort with planned follow-up may have reduced the level of anxiety, leading to underestimation of this parameter. Nevertheless, one should notice that the hypothesis of functional somatic disorder, which is defined by symptoms being insufficiently explained by impairment of the organs that they designate (e.g., dyspnea with no respiratory impairment) is not called into question by these results on general anxiety. Indeed, among the different cognitive and behavioral mechanisms involved in functional somatic disorders, illness attribution, and catastrophic beliefs, which may influence the perception of bodily perceptions, and behavioral avoidance (including physical activity cessation), which may influence the course of these symptoms, constitute two major factors (35) that are not assessed by the HAD-S depression and anxiety subscales. Among the available tools, the somatic symptom disorder-B criteria scale [SSD-12, (36)] is a validated scale that accurately explore the specific psychological features associated with functional somatic disorders. Future studies would benefit from specific assessment of these cognitive and behavioral mechanisms.

Some strengths of our study should be underlined. We used a prospective design with a 3-month follow-up of COVID-19 survivors and provide an original approach in exploring the association between anxiety or depression and persistent physical symptoms within COVID-19 survivors. This prospective design allowed us to explore the presence of predictive factors, previously and independently assessed from the clinical outcomes. We also used HAD-S, a valid and reliable scale, which does not include an assessment of physical symptoms (37): we could thus distinguish the psychiatric symptoms evaluated by our scale, and the physical symptoms evaluated during a clinical interview.

However, our study also has some limitations: the monocentric recruitment of hospitalized patients only and the selection biases that makes the sample non-representative of all patients with severe COVID-19, the limited sample size that reduce statistical power, and the observational design that does not allow concluding on causal links. Furthermore, all the included patients were hospitalized during the pandemic first wave and may not be representative of patients who had severe COVID-19 later on. As we tested six hypotheses (i.e., six possible interactions), the significant depression by pain interaction would not have survived correction for multiple tests. In addition, our data contained few biological variables, despite the potential confounding nature of certain biological variables such as the level of cortisol or specific inflammatory cytokines for persistent physical symptoms. We were also not able to take into account any potential past history of depression or other psychiatric disorder, as well as data regarding interpersonal functioning. Furthermore, the sample size did not allow to include much variables in the models. These results should trigger further investigations with larger sample size.

**CONCLUSION**

In this study, we did not find that anxiety at 1 month after hospitalization was associated with persistent physical symptoms at 3 months in patients hospitalized for COVID-19. However, we found that having a greater depression score and a prior pain complaint was nonetheless significantly associated with persistent pain complaint at 3 months, with a similar trend for dyspnea. These
intriguing results must be considered with caution, but may warrant focused attention on depressive symptoms following acute COVID-19. Considering the possibility of treating depressive symptoms effectively and early, this association could be a lever in the management of persistent physical symptoms.

**DATA AVAILABILITY STATEMENT**

The data analyzed in this study is subject to the following licenses/restrictions: personal health data underlying the findings of our study are not publicly available due to legal reasons related to data privacy protection. Requests to access these datasets should be directed to cedric.lemogne@aphp.fr, jean-sebastien.hulot@aphp.fr.

**ETHICS STATEMENT**

The study is part of The French COVID Cohort (NCT04262921) that was authorized by the French Ethics Committee (ID RCB:2020-A00256-33). The patients/participants provided their written informed consent to participate in this study.

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REFERENCES
1. Moreno C, Wykes T, Galderisi S, Nordentoft M, Crosseley N, Jones N, et al. How mental health care should change as a consequence of the COVID-19 pandemic. Lancet Psychiatry. (2020) 7:813–24. doi: 10.1016/S2215-0366(20)30307-2
2. Mizumoto K, Chowell G. Estimating risk for death from coronavirus disease, China, January–February 2020. Emerg Infect Dis. (2020) 26:1251–6. doi: 10.3201/eid2606.200233
3. Cortés-Telles A, López-Romero S, Figueroa-Hurtado E, Pou-Aguilar YN, Wong AW, Milne KM, et al. Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnea. Respir Physiol Neurobiol. (2021) 288:103644. doi: 10.1016/j.resp.2021.103644
4. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kambholz J. Post-COVID-19 fatigue: potential contributing factors. Brain Sci. (2020) 10:1012. doi: 10.3390/brainsci10120112
5. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, et al. “Long-COVID”: a cross-sectional study of persistent symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. (2020) 76(4):396–8. doi: 10.1136/thoraxjnl-2021-251858
6. Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Urbe R, Torralba Y, Alserva-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019(COVID-19): a systematic review and meta-analysis. Chron Respir Dis. (2021) 18:14799731211002240. doi: 10.1177/14799731211002240
7. Matta J, Wiernik E, Cazan H, Cazan-Milea E, Cazan H, Cazan-Milea E, et al. Association of self-reported COVID-19 and SARS-CoV-2 serology results with persistent physical symptoms among French adults during the COVID-19 pandemic. JAMA Int Med. (2021).
8. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens P, et al. Acute COVID-19 syndrome. Nat Med. (2021) 27:601–15. doi: 10.1038/s41591-021-02183-x
9. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. (2019) 594:259–64. doi: 10.1038/s41586-021-03553-9
10. Troidy EA, Kohn JN, Hong S. Are we facing a crashing wave of episode depression. East Asian Arch Psychiatry. (2012) 22(4):146–53.
11. Lam MH-B, Wing Y-K, Yu MW-M, Leung C-M, Ma RCW, Kong APS, et al. Mental morbidity and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. Arch Intern Med. (2009) 169:2142–7. doi: 10.1001/archinternmed.2009.384
12. Wu KK, Chan SK, Ma TM. Posttraumatic stress, anxiety, and depression in survivors of severe acute respiratory syndrome (SARS). J Trauma Stress. (2005) 18:39–42. doi: 10.1002/jts.20004
13. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. (2020) 7:611–27. doi: 10.1016/S2215-0366(20)30203-0
14. Cheng SKW, Wong CW, Tsang I, Wong KC. Psychological distress and negative appraisals in survivors of severe acute respiratory syndrome (SARS). Psychol Med. (2004) 34:1187–95. doi: 10.1017/S003329170002272
15. Lam MH-B, Wing Y-K, Yu MW-M, Leung C-M, Ma RCW, Kong APS, et al. Mental morbidity and chronic fatigue in severe acute respiratory syndrome survivors:long-term follow-up. Arch Intern Med. (2009) 169:2142–7. doi: 10.1001/archinternmed.2009.384
16. Bottemanne H, Delaigue E, Lemogne C. SARS-CoV-2 Psychiatric sequelae: an urgent need of prevention. Front Psychiatry. (2021) 12:1479. doi: 10.3389/fpsyg.2021.738696
17. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollottini I, et al. Anxiety and depression in COVID-19 survivors: role of internal and inflammatory predictors. Brain Behav Immun. (2020) 89:594–600. doi: 10.1016/j.bbi.2020.07.037
18. Barkow K, Heun R, Ustün TB, Maier W. Identification of items which predict later development of depression in primary health care. Eur Arch Psychiatry Clin Neurosci. (2001) 251:11–4. doi: 10.1007/978-3-642-55152-2
19. Alhalal EA, Alhalal IA, Alaida AM, Alshoqayt C, Alzaher AI. Effects of chronic pain on sleep quality and depression: a cross-sectional study. Saudi Med J. (2021) 42:315–23. doi: 10.15537/smj.42.3.20200768
20. Park MJ, Choi KW, Na EJ, Hong JP, Cho MJ, Fava M, et al. Multiple types of somatic pain increase suicide attempts and depression: a nationwide community sample of Korean adults. Compr Psychiatry. (2019) 90:43–8. doi: 10.1016/j.comppsych.2018.12.006
21. Cai X, Hu X, Ekumi IO, Wang J, An Y, Li Z, et al. Psychological distress and its correlates among COVID-19 Survivors during early convalescence among age groups. Am J Geriatr Psychiatry. (2020) 28:1030–9. doi: 10.1016/j.jagp.2020.07.003
22. Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. Brain Behav Immun. (2020) 88:17–27. doi: 10.1016/j.bbi.2020.05.038
23. Grover S, Kumar V, Chakraborti S, Hollickati P, Singh P, Tyagi S, et al. Prevalence and type of functional somatic complaints in patients with first-episode depression. East Asian Arch Psychiatry. (2012) 22(4):146–53.
24. Nielsen H, Engberg J, Ejlertsen T, Nielsen H. Psychometric scores and persistence of irritable bowel after Campylobacter concius infection. Scand J Gastroenterol. (2014) 49:545–51. doi: 10.3109/0305242X.2014.886718
25. Grover S, Kumar V, Chakraborti S, Hollickati P, Singh P, Tyagi S, et al. Psychological distress and type of functional somatic complaints in patients with first-episode depression. Compr Psychiatry. (2019) 90:43–8. doi: 10.1016/j.comppsych.2018.12.006
26. Cai X, Hu X, Ekumi IO, Wang J, An Y, Li Z, et al. Psychological distress and its correlates among COVID-19 Survivors during early convalescence among age groups. Am J Geriatr Psychiatry. (2020) 28:1030–9. doi: 10.1016/j.jagp.2020.07.003
27. Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. Brain Behav Immun. (2020) 88:17–27. doi: 10.1016/j.bbi.2020.05.038
28. Grover S, Kumar V, Chakraborti S, Hollickati P, Singh P, Tyagi S, et al. Prevalence and type of functional somatic complaints in patients with first-
28. Gouraud C, Bottemanne H, Lahlou-Laforêt K, Blanchard A, Günther S, Batti SE, et al. Association between psychological distress, cognitive complaints, and neuropsychological status after a severe COVID-19 episode: a cross-sectional study. Front Psychiatry. (2021) 12:725861. doi: 10.3389/fpsyt.2021.725861

29. Bocèrèan C, Dupret E. A validation study of the Hospital Anxiety and Depression Scale (HADS) in a large sample of French employees. BMC Psychiatry. (2014) 14:354. doi: 10.1186/s12888-014-0354-0

30. Roberts SR, Bonnici DM, Mackinnon AJ, Worcester MC. Psychometric evaluation of the Hospital Anxiety and Depression Scale (HADS) among female cardiac patients. Br J Health Psychol. (2001). 6(Pt 4):373–83. doi: 10.1348/135910701169278

31. Djukanovic I, Carlsson J, Årestedt K. Is the Hospital Anxiety and Depression Scale (HADS) a valid measure in a general population 65-80 years old? A psychometric evaluation study. Health Qual Life Outcomes. (2017) 15:193. doi: 10.1186/s12955-017-0759-9

32. Wu Y, Levis B, Sun Y, He C, Krishnan A, Neupane D, et al. Accuracy of the Hospital Anxiety and Depression Scale Depression subscale (HADS-D) to screen for major depression: systematic review and individual participant data meta-analysis. BMJ. (2021) 373:n972. doi: 10.1136/bmj.n972

33. Coen SJ, Kano M, Farmer AD, Kumari V, Giampietro V, Brammer M, et al. Neuroticism influences brain activity during the experience of visceral pain. Gastroenterology. (2011). 141:909.e1–17.e1. doi: 10.1053/j.gastro.2011.06.008

34. Kadimpati S, Zale EL, Hooten MW, Ditre JW, Warner DO. Associations between neuroticism and depression in relation to catastrophizing and pain-related anxiety in chronic pain patients. PLoS ONE. (2015) 10:e0126351. doi: 10.1371/journal.pone.0126351

35. Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. Clin Psychol Rev. (2007) 27:781–97. doi: 10.1016/j.cpr.2007.07.002

36. Toussaint A, Murray AM, Voigt K, Herzog A, Gierk B, Kronke K, et al. Development and validation of the somatic symptom disorder-B criteria scale (SSD-12). Psychosom Med. (2016) 78:5–12. doi: 10.1097/PSY.0000000000000240

37. Norton S, Cosco T, Doyle F, Done J, Sacker A. The Hospital Anxiety and Depression Scale: a meta confirmatory factor analysis. J Psychosom Res. (2013) 74:74–81. doi: 10.1016/j.jpsychores.2012.10.010

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