Original Article
2025, 15(1): 57-66
DOI: 10.22038/EBCJ.2025.82160.3033

Received: 13/09/2024
Accept & ePublished: 09/03/2025

Evidence Based Care Journal
http://ebcj.mums.ac.ir
Online ISSN: 2008-370X

Correlation of Inflammatory Biomarkers with Neuropsychological Performance of COVID-19 Survivors After ICU Discharge: 20 Months Follow-up

Samaneh Sadat Asadi Kakhki [1], Ghazaleh Elahabadi [2], Mahdieh Jafari [3], Hojat Naghavai [3], Mahyar Mohseni Birjandi [4], Benyamin Fazli [5*]

Abstract

Background: COVID-19 infection may be related to development of neural damage and neural inflammation. Accumulating evidence highlighted the high prevalence of long-term mental health problems among COVID-19 survivors.

Aim: The present study was conducted with aim to evaluate the long-term psychosomatic effects of COVID-19 and their relationship with inflammatory biomarkers among COVID-19 survivors after ICU discharge.

Method: This prospective study was conducted on patients discharged from the COVID-19 intensive care unit (ICU) between June and August 2021. Depression, anxiety, health anxiety, sleep quality and cognitive abilities were assessed. Also, inflammatory biomarkers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Neutrophil-to-lymphocyte ratio (NLR), ferritin and D-dimer were measured. Data were analyzed using SPSS (version 22.0) and Pearson correlation analysis and multiple linear regression analysis. $p<0.05$ was considered significant.

Results: Among 78 survivors, 26% and 45.5% had moderate/severe degree of depressive and anxiety symptoms, respectively. Moreover, 25% of participants reported health anxiety and 61.8% poor sleep quality. The cognitive abilities had a significant inverse correlation with D-dimer level (r=-0.44, $p<0.001$). Moreover, BDI-II score was significantly correlated with ESR level (r=0.29, $p<0.06$). The only factor associated with BDI-II depression score was ESR levels (β=0.37, p=0.013). D-dimer was independently associated with cognitive abilities score (β=-0.45, p=0.001).

Implications for Practice: Although there was a high prevalence of mental disorders among patients discharged from COVID-19 ICUs even after 20 months, our results do not support a dominant role for inflammatory background (during acute phase of COVID-19) to explain the neuropsychological impairments long time after COVID-19 infection.

Keywords: Inflammation, Pandemic, Psychological problem, SARS-CoV-2

1. Anesthesiologist, Department of Anesthesiology, Mashhad university of Medical Sciences, Mashhad, Iran
2. Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
3. Assistant professor of Anesthesiology, Department of Anesthesiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
4. General physician, Mashhad University of Medical Sciences, Mashhad, Iran
5. Assistant Professor of Anesthesiology and Critical Care Medicine, Department of Anesthesiology, Mashhad university of Medical Sciences, Mashhad, Iran

* Corresponding Author Email: fazlib@mums.ac.ir

Introduction

The COVID-19 pandemic had deteriorating effects on global health, with far-reaching consequences that extend beyond the immediate physical manifestations of the disease (1). One important area of concern is the long-term psychiatric effects of the disease, particularly among cases who have experienced severe involvement and higher inflammatory levels during the course of the disease (2). Accumulating evidence highlighted the alarmingly high prevalence of long-term mental-related problems among COVID-19 survivors. Previous studies reported depression, anxiety, health anxiety, as well as sleep disturbances as some of the most debilitating psychological distress experienced by this population (3). In particular, vulnerable patients group comprises those who have been admitted to intensive care units (ICUs) due to severe COVID-19 complications. As these cases undergone the difficult path to recovery, they often face a myriad of ongoing mental health challenges (4). The mental health crisis developed by the pandemic is overwhelming, with studies demonstrating cognitive impairment in 20-57% of cases, and mental health problems, primarily anxiety and depression in 6-60% of ICU survivors (5). Furthermore, a UK-based study found that 40% of patients experienced depression, with 79% of those individuals also exhibiting anxiety symptoms (6). Remarkably, 18% of all patients were found to have all the symptoms (7).

In a study on COVID-19 patients with one-month follow-up after hospital discharge, the increments in psychiatric complications varied from 10-35%. The baseline Systemic Immune Inflammation Index was positively correlated with the depression and anxiety scores (8). COVID-19 infection has been found to cause neural damage (9), and neural inflammation, especially in cases who have experienced a cytokine storm, which plays a considerable role in the appearance of psychiatric manifestations (10). There are several studies evaluating the relationship between inflammatory biomarkers and short-term or mid-term psychiatric consequences of the COVID-19, but the results are inconsistent (11-13). The present study was conducted with aim to evaluate the long-term psychosomatic effects of COVID-19 and their relationship with inflammatory markers among patients who have been discharged from COVID-19 ICUs in Iran.

Methods

This prospective study was conducted on patients who were admitted to the COVID-19 ICUs of Imam Reza hospital in Mashhad (Northeast of Iran), and eventually discharged from the hospital during the fifth wave of the pandemic (between June and August 2021). Inclusion criteria were age ≥ 18 years, ICU hospitalization for COVID-19 infection and discharge to home care. Individuals with a history of psychological disorders, malignancies, autoimmune disorders, and hepatic or renal failure were excluded from the study.

Approximately one to two days prior to discharge, the physicians approached the participants and provided an exact explanation of the study. This timeline allowed the subjects enough time to consider make an informed decision about involvement in the study. Written informed was obtained for participation in the study. Additionally, the researchers used the clinical records to obtain relevant demographic, clinical and laboratory characteristics. This laboratory measurement data collection is an approach based on existing information, minimizing the burden on participants and increasing the efficiency of the research process.

To assign a baseline value, the blood test results requested on the admission day or the next day were checked retrospectively from the hospital information system and the indices that may be related to inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Neutrophil-to-lymphocyte ratio (NLR), ferritin and D-dimer levels) were recorded. All participants were follow-up by telephone 20 months post-discharge, with a comprehensive protocol examining depression, anxiety and health anxiety symptoms, cognitive abilities and sleep quality. The tools used to collect data were The Cognitive Ability Questionnaire (CAQ), The Beck Depression Inventory (BDI-II), The Hamilton Anxiety Rating Scale (HAM-A), The Health Anxiety Inventory (HAI), and The Pittsburgh Sleep Quality Index (PSQI).

The Cognitive Ability Questionnaire (CAQ) consists of 30 questions, each with a Likert-type scale ranging from "never" (score 1) to "always" (score 5). This scale is used to measure a broad spectrum of cognitive abilities, including memory, attention, inhibitory control, decision-making, planning, social cognition, and cognitive flexibility. The higher the overall score, the better the individual's cognitive performance. The CAQ's reliability and validity have been well-established, with the

subscales demonstrating good internal consistency, as indicated by Cronbach's alpha values ranging from 0.71 to 0.85 (14).

The Beck Depression Inventory (BDI-II) has been extensively used to evaluate depression in different contexts and population. The BDI-II comprises 21 items, each scored on a 4-point Likert scale, ranging from 0 to 3. Higher scores indicate a more severe depressive state. Depression was defined as a BDI-II score of 14 or higher, which corresponds to at least mild depression according to Beck's categories for the instrument. This definition was further subdivided into three categories: mild (score of 14-19), moderate (score of 20-28), and severe (score of 29-63) (15).

The Hamilton Anxiety Rating Scale (HAM-A) is a widely recognized clinician-administered instrument designed to quantify the severity of anxiety symptoms. This comprehensive scale comprises 14 items, each evaluated on a 5-point Likert scale, resulting in a total score ranging from 0 to 56. Higher scores on the HAM-A indicate more severe anxiety. Responders based on HAM-A scores are typically categorized into four groups. Individuals scoring below 8 are considered to have no clinically significant anxiety, while those with scores between 8 and 14 are classified as experiencing mild anxiety. Moderate anxiety is characterized by scores ranging from 15 to 23, and severe anxiety is indicated by scores exceeding 24 (16).

The Health Anxiety Inventory (HAI) serves as a tool to assess an individual's concerns regarding their health and the presence of hypochondriacal symptoms. The short version of this inventory comprises 18 items that explore anxiety-related aspects of health. The scoring system for the HAI ranges from 0 to 3 for each question, culminating in a total score between 0 and 54, with a score of 0-18 indicating low anxiety, 18-36 signifying medium, and a score above 36 suggesting severe anxiety. The validity and reliability of the HAI for the Persian version have been previously reported (16).

The Pittsburgh Sleep Quality Index (PSQI) has emerged as a widely recognized tool for evaluation of sleep patterns and disturbances. This self-reported questionnaire examines sleep quality over a one-month period. The PSQI encompasses 19 items that are ultimately combined to yield seven distinct component scores. This tool offers a robust assessment of an individual's sleep quality by summing up these factors into a global PSQI score ranging from 0 to 21. PSQI score exceeding 5 is generally indicative of poor sleep quality, with higher scores signifying more severe sleep disturbances. The Persian version of the PSQI which has demonstrated strong psychometric properties previously was used in this study (17).

Data were analyzed using SPSS (version 22.0) (SPSS Inc., USA). Pearson correlation analysis was recruited to detect correlation between variables. Furthermore, the multiple linear regression analysis with the Stepwise method was used to find the potential predictors of different mental health issue. $p<0.05$ was considered significant.

Ethical Consideration

The study was approved by the Ethnic Committee of Mashhad University of Medical Sciences (ethical code: IR.MUMS.MEDICAL.REC.1400.849).

Results

Among the 78 participants, 39 (50.0%) were female. The mean age of the participants was 45.2±11.0 years (ranging 26-65 years) and their BMI was 29.2±4.6 kg/m^2 (ranging 19.3-39.0 kg/m^2). A total of 28 (36.1%) of the participants had a Diploma degree, 74 (94.6%) were married, 12 (15.4%) were smoker, and 43 (55.1%) of the participants had chronic disease (Table 1).

The mean score of CAQ was 81.0±23.7 (range 61-140). The mean scores on the BDI-II for depression and the PSQI for sleep quality for all subjects were 14.0±11.1 and 5.8±3.6, respectively. Of the participants, 61.8% had sleep quality higher than or equal to 5 points, indicating sleep problems. In BDI-II, 54.5% with 0–13 points, 19.5% with 14-19 points, 15.6% with 20-28 points, 10.4% with 29-63 points, of which 35 individuals (45.5%) had different degrees of depression symptoms (Figure 1).

The mean score of anxiety was 14.4±9.9 which was above the cut-off point for anxiety and 70.1% of individuals had anxiety. The mean score of health anxiety was 13.7±9.2 and 25% of the participants had mild depression moderate/severe health anxiety (Figure 1). The proportion of patients experiencing one or a combination of four mental distresses is presented in Figure 2. Regarding a total of four mental problems including depression, anxiety, health anxiety and poor

sleep quality, 27.5% of participants experienced none, 21.9% had one, as well as 27.4%, 16.4% and 6.8% suffered from combination of two, three or four complications, respectively.

Table 1. General characteristics of the study participants

Variables	N (%)
Age	
<40 years	34 (44)
≥40 years	44 (56)
BMI (kg/m^2)	
<18.5	0 (0)
18.5-24.9	15 (19.2)
25-29.9	31 (39.7)
≥30	32 (41.0)
Sex	
Male	39 (50)
Female	39 (50)
Marital status	
Married	74 (94.6)
Single	2 (2.7)
Divorced	2 (2.7)
Family member (n)	
<4	46 (59.0)
4-6	31 (39.7)
≥7	1 (1.3)
Educational level	
Under Diploma	25 (31.9)
Diploma	28 (36.1)
Associate degree	4 (5.6)
Bachelor's degree	7 (8.3)
Master's degree	
Chronic disease	
Yes	43 (55.1)
No	35 (44.9)
Smoker	
Yes	12 (15.4)
No	66 (84.6)

The correlation between neuropsychological variables was assessed using Pearson correlation analysis (Table 2). There was positive correlation between scores of BDI-II, HAM-A, HAI and PSQI ($p<0.005$). Furthermore, score of cognitive abilities negatively correlated with scores of BDI-II, HAM-A, HAI and PSQI ($p<0.05$).

Correlation analysis revealed that cognitive abilities had significant inverse correlation with D-dimer level ($r=-0.44$, $p<0.001$). Moreover, BDI-II score was significantly correlated with ESR level ($r=0.29$, $p<0.06$) (Table 3).

Table 2. Correlation matrix between neuropsychological variable using Pearson correlation analysis

Variable		Cognitive abilities	Depression	Anxiety	Health anxiety
Depression	r	-0.67			
	p	<0.001			
Anxiety	r	-0.44	0.68		
	p	<0.001	<0.001		
Health	r	-0.31	0.53	0.57	
anxiety	p	0.011	<0.001	<0.001	
Sleep	r	-0.24	0.35	0.47	0.31
problems	p	0.045	0.002	<0.001	0.006

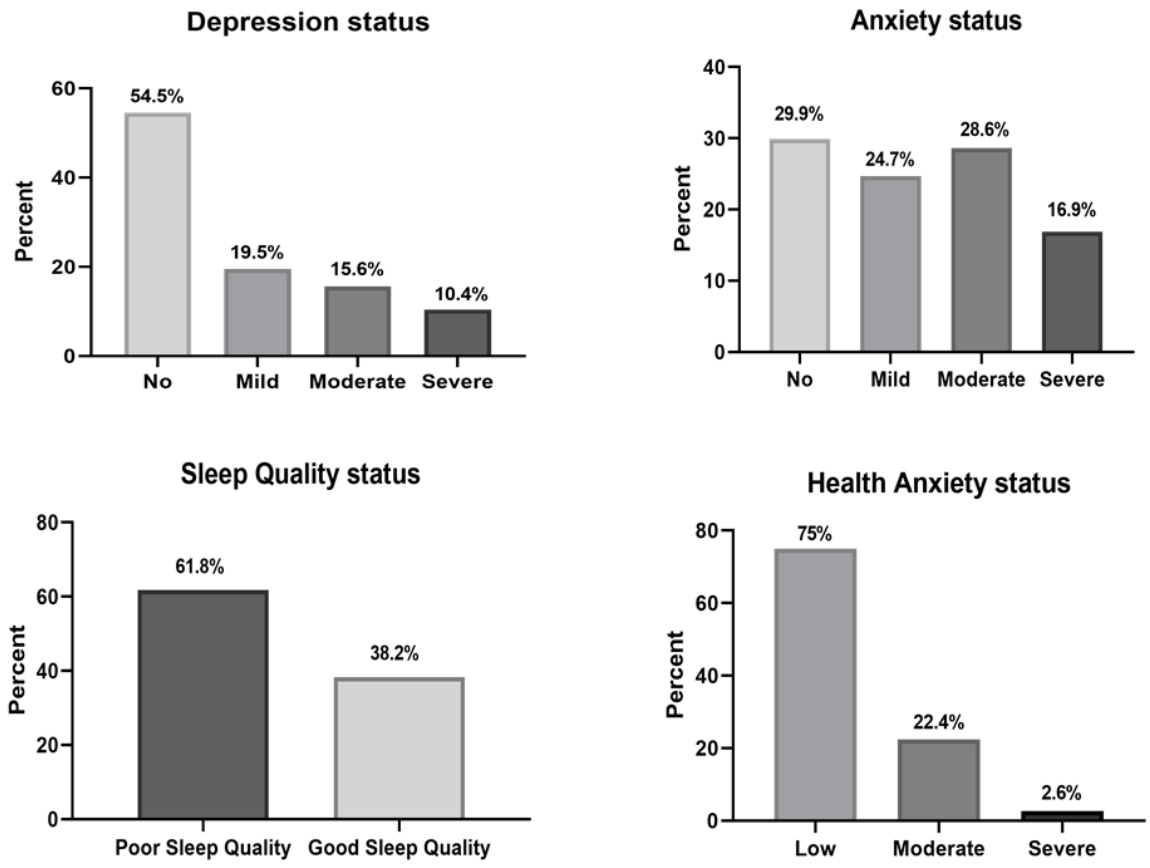

Figure 1. Prevalence of depression, anxiety, health anxiety and sleep disorders among COVID ICU survivors after 20 months follow-up

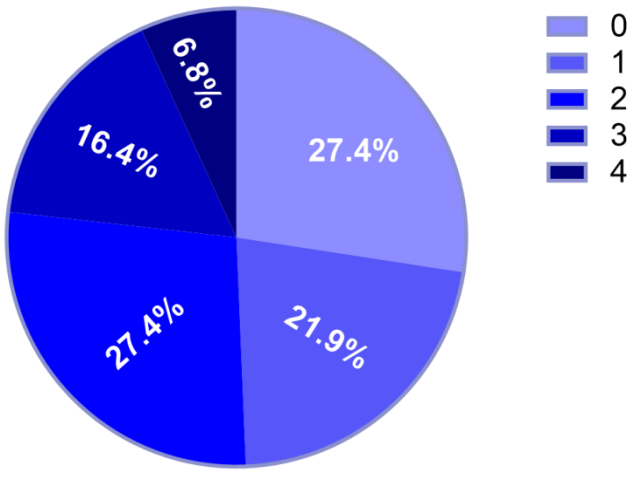

Figure 2. The proportion of individuals experiencing none, one or a combination of four mental distresses including depression, anxiety, health anxiety and poor sleep quality

Table 3. Correlation coefficient between neuropsychological tests and laboratory measurements

Variables	Cognitive abilities r	Depression r	Anxiety r	Health Anxiety r	Sleep quality r
ESR	0.11	0.29*	0.21	0.20	0.11
CRP	0.24	0.12	0.11	0.11	0.12
NLR	-0.16	-0.42	-0.09	-0.14	-0.07
Ferritin	-0.23	0.08	0.001	-0.26	-0.04
D-dimer	-0.44***	-0.08	-0.014	-0.11	-0.15

Abbreviations: erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); Neutrophil-to-lymphocyte ratio (NLR).
*p<0.05; **p<0.01; ***p<0.001

On multivariate analysis, the only factor associated with BDI-II depression score was ESR levels (linear regression coefficient 0.37, p=0.013). Moreover, the factor independently associated with cognitive abilities score was D-dimer (linear regression coefficient -0.45, p=0.001).

Discussion

The purpose of the present study was to comprehensively evaluate the long-term psychosomatic effects of COVID-19 and their association with inflammatory biomarkers in COVID-19 survivors after ICUs discharge. Overall, 26%, 45.5% 25% and 38.2% of the participants demonstrated moderate to severe degree of depressive, anxiety, health anxiety and sleep problems symptoms, respectively. Depression, a condition defined by constant feelings of sadness, hopelessness, and a loss of interest in routine activities, has emerged as a significant concern. This is an obvious contrast to pre-pandemic depression levels, highlighting the great impact of the COVID-19 experience on an individual's mental well-being (18). Alongside depression, anxiety disorders have also been widely documented among COVID-19 ICU survivors (19). Generalized anxiety, characterized by excessive worry and tension, as well as more specific forms of anxiety, such as health anxiety, have been reported at alarmingly high rates (20). Health anxiety, in particular, has become an urgent issue, as individuals who have endured the distressing experience of severe COVID-19 often develop an amplified fear of illness and an elevated sensitization with their physical health (21).

Previous studies reported the prevalence rates of anxiety and depression and cognitive impairment reaching as high as 23%, 26% and 57%, respectively, even 6-12 months after initial infection (22, 23). The situation is particularly serious for individuals who have experienced severe cases of COVID-19, with reports of cognitive impairments, mental health issues, and poor sleep quality persisting long after initial recovery (5). Evidences indicated that the rate of anxiety and depressive symptoms in the 12-14 months follow-up of ICU admission was 34% and 29%, respectively (24, 25). Gramaglia et al. reported that the prevalence of anxiety and depression was 34.5% and 32%, respectively at four months after hospital discharge due to the COVID-19 infection. Interestingly, the rate of depression and anxiety reduced to 16.9% and 19.1%, respectively after 12-months (26). This inconsistency between the results may be due to the timing and procedure of the measurement in different studies. The effect of COVID-19 hospitalization on mental distress has been globally mitigated over time. However, many extra and confounding factors may occur in such a prolonged time. Furthermore, the disruption to sleep patterns is another prevalent complication reported by COVID-19 ICU survivors. Insomnia, fragmented sleep, and overall poor sleep quality have been consistently found in this population. Neville and colleagues reported that the prevalence of sleep disturbances was 50.8% at 6 months post-discharge from ICU (27). In another survey, 75% of COVID-19 ICU survivors reported poor sleep quality after 3 months follow-up (28).

There are reasons multifaceted and complex for these long-term mental health challenges. The traumatic nature of the COVID-19 experience, the physical complications of the disease, the isolation and disruption to daily life, and the uncertainty about long-term prognosis all play role in the formation and persistence of these psychological problems (29). Patients afflicted with prolonged or post-COVID syndrome have reported a range of debilitating symptoms, including faint, tiredness, depression, sleep complications, loss of concentration, and memory problems (30, 31). While the precise cause of these persistent symptoms remains ambiguous, evidence indicates that they may be linked to the underlying inflammation that persists even after the initial infection has resolved. The

presence of virus particles in the lungs, particularly in cases of severe COVID-19, can contribute to a state of chronic inflammation (31, 32). This inflammation, in turn, may activate the complement system and lead to the formation of micro- and macro-thrombi, or blood clots. Furthermore, the dysregulation of cytokines, which are signaling molecules playing a main role in the body's immune response, has been linked to the pathogenesis of certain psychiatric disorders (33, 34).

ESR serves as a general marker of inflammation, while CRP is a more specific indicator, reflecting the presence of acute-phase proteins. The NLR provides insights into the balance between these two essential immune cell types, which can shift during periods of inflammation. Ferritin, a protein involved in iron storage, and D-dimer, a fibrin degradation product, are additional markers that may contribute to the overall assessment of the patient's condition (35). The retrospective analysis of these specific blood test indices offers a comprehensive approach to understand the inflammatory status of patients at the time of COVID-19 admission.

In the present study, BDI-II depression score only correlated with ESR level. Consistent with this finding, Sun et al. observed no association between NLR and depression-anxiety levels in patients with COVID-19 (11). Similarly, in a study among COVID-19 patients who were not ICU admission, depression-anxiety scores were not related with NLR-CRP values (36). In contrast, Khorasanchi et al. reported a positive relationship between depression, anxiety, stress symptoms and hematological inflammatory biomarkers such as platelet-lymphocyte ratio and red cell distribution width (13). This difference in the results may be due that the inflammatory response is a complicated process influenced via many variables.

Coronaviruses have neurotropic properties and “cytokine storms” contribute to neuroinflammation not only in the periphery but also in the central nervous system, leading to mental complications (37, 38). Complex interaction of immunological axes, worry about infection, unsure of the future, stigma, and physical distancing affected patients during the pandemic are important mental stressors which can elevate the systemic inflammatory state (39, 40).

In the present study, higher D-dimer concentrations were related to worsened cognitive abilities. Along with this finding, Moretta et al. in their study reported that post-COVID-19 patients with reduced cognitive efficiency had elevated levels of D-Dimer (41). Recently, a study on 40 COVID-19 patients revealed a correlation between elevated D-dimer levels and poorer cognitive performance (42). In a similar research by Frontera et al., a significant association was found between neurodegenerative biomarkers and the D-dimer that may provide valuable insights into the mechanisms underlying the acute brain injury experienced by some COVID-19 patients. It has been suggested that the signs of acute COVID-19, hypoxia and hyperinflammation, may contribute to the development of Alzheimer's-like pathology in non-COVID-19 populations. This occurs through the over-expression of enzymes in the amyloidogenic axis and the down-expression of proteins responsible for breaking down amyloid-beta (Aβ) (43). Additionally, higher D-dimer levels during the acute illness phase were associated with lower verbal recall and psychomotor speed (12).

The high prevalence of mental disorders among post-COVID-19 patients indicated the importance of early identification and intervention. Rigorous screening and regular mental health assessments, both during the hospitalization and in the post-discharge period, can help to identify those at risk and facilitate timely access to appropriate care. Moreover, the insights obtained from this study emphasize the establishment of appropriate support systems and preventive measures to reduce the long-term psychological impact of the pandemic. This knowledge can also contribute to the design of more effective public health strategies and developing a more resilient and adaptable community in the face of future health crises. Comprehensive and integrated care models, which consist of wide spectra of evidence-based interventions, are important to support these populations in their recovery process. This may include a combination of psychotherapy, medication management, support groups, and targeted rehabilitation programs to address the specific challenges of these individuals.

Similar to other investigations, this study had some limitations. There was no pre-COVID-19 baseline data regarding the mental health status of participants. Also, neuropsychological assessment was conducted by phone, which is fewer reliable compared to assessment in a clinic. It is suggested to perform more studies in the future considering these limitations.

Implications for practice

Although a high prevalence of mental disorders was identified among patients discharged from COVID-19 ICUs even after 20 months, our results do not support a dominant role for inflammatory background (within acute phase of COVID-19) to explain the neuropsychological impairments long-time after COVID-19 infection. These findings also indicate potential interventions for mental distress following COVID-19 that future investigations might address.

Acknowledgments

The authors would like to thank the Vice Chancellor for Research of Mashhad University of Medical Sciences for supporting this research. We also thank Nooshin Abdollahpour who provided technical help and writing assistance.

Conflicts of interest

The authors declared no conflict of interest.

Funding

The study is supported by Mashhad University of Medical Sciences.

Authors' Contributions

Samaneh Sadat Asadi Kakhki designed the study and performed data collection. Ghazaleh Elahabadi performed the intervention. Mahdieh Jafari participated in designing the study and data collection. Hojat Naghavai and Mahyar Mohseni Birjandi performed data collection. Benyamin Fazli performed the study designing, data collection, carrying out the intervention, and writing the manuscript. All authors reviewed and approved the final manuscript.

References

1. Joshee S, Vatti N, Chang C, editors. Long-term effects of COVID-19. Mayo Clinic Proceedings; Elsevier. 2022; 97(3): 579-9.
2. Mazza MG, Palladini M, De Lorenzo R, Magnaghi C, Poletti S, Furlan R, et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. Brain, behavior, and immunity. 2021;94:138-47.
3. Iqbal SZ, Li B, Onigu-Otito E, Naqvi MF, Shah AA. The long-term mental health effects of COVID-19. Psychiatric Annals. 2020;50(12):522-5.
4. Klinkhammer S, Horn J, Duits AA, Visser-Meily JM, Verwijk E, Slooter AJ, et al. Neurological and (neuro) psychological sequelae in intensive care and general ward COVID-19 survivors. European journal of neurology. 2023;30(7):1880-90.
5. Nakanishi N, Liu K, Kawakami D, Kawai Y, Morisawa T, Nishida T, et al. Post-intensive care syndrome and its new challenges in coronavirus disease 2019 (COVID-19) pandemic: a review of recent advances and perspectives. Journal of clinical medicine. 2021;10(17):3870. doi.org/10.3390/jcm10173870
6. Hatch R, Young D, Barber V, Griffiths J, Harrison DA, Watkinson P. Anxiety, depression and post traumatic stress disorder after critical illness: a UK-wide prospective cohort study. Critical care. 2018;22:1-13.
7. Tripathy S, Acharya SP, Singh S, Patra S, Mishra BR, Kar N. Post traumatic stress symptoms, anxiety, and depression in patients after intensive care unit discharge–a longitudinal cohort study from a LMIC tertiary care centre. BMC psychiatry. 2020;20:1-11.
8. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain, behavior, and immunity. 2020;89:594-600.
9. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses. 2019;12(1):14. doi.org/10.3390/v12010014
10. Dantzer R. Neuroimmune interactions: from the brain to the immune system and vice versa. Physiological reviews. 2018;98(1):477-504.
11. Sun YJ, Feng YJ, Chen J, Li B, Luo ZC, Wang PX. Clinical features of fatalities in patients with

COVID-19. Disaster medicine and public health preparedness. 2021;15(2):e9-11.
12. Miskowiak KW, Johnsen S, Sattler SM, Nielsen S, Kunalan K, Rungby J, et al. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. European Neuropsychopharmacology. 2021;46:39-48.
13. Khorasanchi Z, Rashidmayvan M, Hasanzadeh E, Moghadam MR, Afkhami N, Asadiyan-Sohan P, et al. The association of hematological inflammatory markers and psychological function in COVID-19 patients: A cross-sectional study. Physiological Reports. 2023;11(24):e15889. doi.org/10.14814/phy2.15889
14. Nejati V. Cognitive abilities questionnaire: Development and evaluation of psychometric properties. Advances in Cognitive Science. 2013;15(2):11-9.
15. Rajabi G, Karju Kasmai S. Psychometric properties of a Persian language version of the beck depression inventory second edition. Quarterly of Educational Measurement. 2012;3(10):139-58.
16. Rabiei M, Kalantari M, Asgari K, Bahrami F. Factor structure analysis, validity and reliability of the health anxiety inventory short form. Journal of Depression and Anxiety. 2013;2: 1. doi:10.4172/2167-1044.1000125
17. Farrahi Moghaddam J, Nakhaee N, Sheibani V, Garrusi B, Amirkafi A. Reliability and validity of the Persian version of the Pittsburgh Sleep Quality Index (PSQI-P). Sleep and Breathing. 2012;16:79-82.
18. Benke C, Asselmann E, Entringer TM, Pané-Farré CA. The role of pre-pandemic depression for changes in depression, anxiety, and loneliness during the COVID-19 pandemic: results from a longitudinal probability sample of adults from Germany. European Psychiatry. 2022;65(1):e76. doi: 10.1192/j.eurpsy.2022.2339
19. Piras I, Piazza MF, Piccolo C, Azara A, Piana A, Finco G, et al. Experiences, emotions, and health consequences among COVID-19 survivors after intensive care unit hospitalization. International journal of environmental research and public health. 2022;19(10):6263. doi: 10.3390/ijerph19106263.
20. Martins S, Ferreira AR, Fernandes J, Vieira T, Fontes L, Coimbra I, et al. Depressive and anxiety symptoms in severe COVID-19 survivors: A prospective cohort study. Psychiatric Quarterly. 2022;93(3):891-903.
21. Heinen A, Varghese S, Krayem A, Molodynski A. Understanding health anxiety in the COVID-19 pandemic. International Journal of Social Psychiatry. 2022;68(8):1756-63.
22. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. The lancet. 2021;398(10302):747-58.
23. Xie Y, Xu E, Al-Aly Z. Risks of mental health outcomes in people with covid-19: cohort study. BMJ. 2022;376: e068993. doi: 10.1136/bmj-2021-068993..
24. Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. General hospital psychiatry. 2016;43:23-9.
25. Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ, et al. Depressive symptoms after critical illness: a systematic review and meta-analysis. Critical care medicine. 2016;44(9):1744-53.
26. Gramaglia C, Gattoni E, Gambaro E, Bellan M, Balbo PE, Baricich A, et al. Anxiety, stress and depression in COVID-19 survivors from an Italian cohort of hospitalized patients: results from a 1-year follow-up. Frontiers in psychiatry. 2022;13:862651. doi: 10.3389/fpsyt.2022.862651. eCollection 2022.
27. Neville TH, Hays RD, Tseng C-H, Gonzalez CA, Chen L, Hong A, et al. Survival after severe COVID-19: long-term outcomes of patients admitted to an intensive care unit. Journal of intensive care medicine. 2022;37(8):1019-28.
28. Rousseau A-F, Minguet P, Colson C, Kellens I, Chaabane S, Delanaye P, et al. Post-intensive care syndrome after a critical COVID-19: cohort study from a Belgian follow-up clinic. Annals of intensive care. 2021;11:1-9.
29. Yıldızeli SO, Kocakaya D, Saylan YH, Tastekin G, Yıldız S, Akbal Ş, et al. Anxiety, Depression, and Sleep Disorders After COVID-19 Infection. Cureus. 2023;15(7): e42637. doi: 10.7759/cureus.42637.
30. Solomon T. Neurological infection with SARS-CoV-2—the story so far. Nature Reviews

Neurology. 2021;17(2):65-6.
31. Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the mystery surrounding post-acute sequelae of COVID-19. Frontiers in immunology. 2021;12:686029. doi.org/10.3389/fimmu.2021.686029
32. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS medicine. 2021;18(9):e1003773. doi: 10.1371/journal.pmed.1003773.
33. Köhler CA, Freitas TH, Maes Md, De Andrade N, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatrica Scandinavica. 2017;135(5):373-87.
34. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature reviews immunology. 2016;16(1):22-34.
35. Pambudi IG, Suryana IK, Rai IB, Kusumawardani IA, Candrawati NW, Sajinadiyasa IG, et al. High Neutrophil to Lymphocyte Ratio, C-Reactive Protein, Procalcitonin and D-dimer as Risk Factors for Severe COVID-19. Medico-Legal Update. 2022;22(1): 41-6.
36. Kahve AC, Kaya H, Okuyucu M, Goka E, Barun S, Hacimusalar Y. Do anxiety and depression levels affect the inflammation response in patients hospitalized for COVID-19. Psychiatry Investigation. 2021;18(6):505-12.
37. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC neurology. 2011;11:1-7.
38. Verstrepen K, Baisier L, De Cauwer H. Neurological manifestations of COVID-19, SARS and MERS. Acta Neurologica Belgica. 2020;120(5):1051-60.
39. Bechter K. Virus infection as a cause of inflammation in psychiatric disorders. Inflammation in Psychiatry. 2013;28:49-60.
40. Clemente I, Sinatti G, Cirella A, Santini SJ, Balsano C. Alteration of inflammatory parameters and psychological post-traumatic syndrome in long-COVID patients. International Journal of Environmental Research and Public Health. 2022;19(12):7103. doi: 10.3390/ijerph19127103.
41. Moretta P, Ambrosino P, Lanzillo A, Marcuccio L, Fuschillo S, Papa A, et al.. Cognitive impairment in convalescent COVID-19 patients undergoing multidisciplinary rehabilitation: the association with the clinical and functional status. Healthcare; 2022: 10(3):480. doi: 10.3390/healthcare10030480..
42. Fitri FI, Darman WR, Ritarwan K. Higher Inflammatory Markers are correlated with Worse Cognitive Function in Coronavirus Disease-2019 Patients. Open Access Macedonian Journal of Medical Sciences. 2022;10(B):1206-11.
43. Frontera JA, Boutajangout A, Masurkar AV, Betensky RA, Ge Y, Vedvyas A, et al. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. Alzheimer's & Dementia. 2022;18(5):899-910.