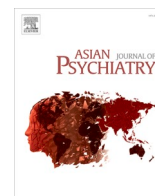




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Letter to the Editor

Psychiatric morbidity among patients attending the post-COVID clinic and its association with hematological inflammatory markers



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Several mechanisms including neural spread, Dysregulated immunomodulation, Immune cell transmigration to the brain, and autoimmunity are proposed as factors contributing to higher psychiatric morbidity among patients with COVID-19 (Banerjee and Viswanath, 2020). Inflammation-related biomarkers, including hematological markers like Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR), have shown an association with several psychiatric disorders (Yuan et al., 2019). Considering these are inexpensive and readily available, exploring their association can add to the early identification and management of psychiatric disorders in patients after COVID-19.

Hence a cross-sectional study was conducted after the first wave of COVID (Data collected between September 2020 to August 2021) at a tertiary care institute after ethical approval (AIIMS/IEC/2020-21/3070). The patients who reported 3–6 months after COVID infection to the post-COVID clinic during the study period were included after written informed consent. Patients with a history of psychiatric illness before COVID-19 were excluded. We collected their sociodemographic data and clinical details (from hospital records for patients admitted to our institute). The disease severity classification was done as per government guidelines (Ministry of Health and Family Welfare, 2020). A psychiatrist evaluated the patients with a semi-structured proforma and clinical interview and the Depression, Anxiety, and Stress Scale – 21 (DASS-21) (Lovibond and Lovibond, 1995). Psychiatric diagnosis was made as per ICD-10 criteria. The hematological Inflammatory markers were calculated, including NLR, PLR, and Systemic Immune-inflammation Index (SII), from a hemogram done at the assessment time.

Out of examined 177 patients, 13 were excluded due to past psychiatric illness. The majority of patients ($n = 164$) were middle-aged (Mean-47.47 years), male (75 %), and educated ≥ 12 th standard (72 %), and 110 patients were admitted to our center during COVID. Out of 110, a majority (56.36 %) had mild symptoms of COVID-19, followed by moderate (23.63 %) and severe (15.45 %), and 4.54 % were asymptomatic. The most common symptom during acute COVID illness was shortness of breath, followed by fatigue.

Out of total 164 patients 20.73 % ($n = 34$) were diagnosed with psychiatric illness, and most common diagnosis was depression ($n = 12$) followed by anxiety disorder ($n = 11$), adjustment disorder ($n = 9$), and insomnia ($n = 2$). The patients more frequently reported anxiety symptoms (50.9 %) than stress (37.3 %) or depressive (27.2 %) symptoms. The presence of psychiatric illness was also not associated with age, education, the severity of illness, or symptom presentation during acute infection ($p > 0.05$).

Inflammatory markers didn't correlate with depression, anxiety, and stress scores on the DASS-21 scale or the psychiatric diagnosis. However, age correlated negatively with anxiety and stress (Table 1).

There is a wide variation in the extent of psychiatric morbidity across studies ranging from 5.8 % (Taquet et al., 2021) to 91.2 % (Ahmed et al., 2021). A recent cohort study reported psychiatric morbidity among 37 % of patients, with anxiety disorder being the most common (Damiano et al., 2022). The sampling methods, cross-cultural variation, phase of pandemic, and method used for defining psychiatric morbidity can explain this wide variation.

In our study, psychiatric morbidity didn't correlate with the severity, COVID symptom, sociodemographic variables (except age), family history of COVID-19, or psychiatric illness and substance use. Possibly, a smaller number of patients with moderate and severe COVID affected this finding. Though studies report conflicting results (Ahmed et al., 2021; Magnúsdóttir et al., 2022; Mazza et al., 2021), a recent Brazilian cohort study also reported no association with clinical severity (among patients with Moderate and Severe COVID-19) (Damiano et al., 2022). The finding suggests that all patients require screening for psychiatric illnesses irrespective of the severity of the COVID. The perception of illness severity probably mediated the impact (Huarcaya-Victoria et al., 2021).

In our study, the younger patients experienced significantly more anxiety and stress. Possibly due to uncertainty regarding the long-term consequences of COVID-19, which has psychologically affected younger patients more.

We could not find an association between hematological inflammatory markers and new onset psychiatric illness or psychiatric symptoms.

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Table 1

Correlation of Inflammatory markers, age, and education with scores on The Depression, Anxiety, and Stress Scale - 21 (DASS-21).

Variable	Score on DASS-21 Subscales		
	Depression	Anxiety	Stress
Neutrophil-Lymphocyte Ratio (NLR)	-0.060	-0.066	-0.061
Platelet-Lymphocyte Ratio (PLR)	-0.044	-0.003	-0.064
Systemic immune-inflammation index (SII)	-0.061	-0.064	-0.043
Age	-0.112	-0.234**	-0.169*
Education	-0.019	-0.099	-0.070

* * $p = 0.002$; * $p = 0.025$

In contrast, studies have shown that hematological inflammatory markers are associated with psychiatric symptoms (Huarcaya-Victoria et al., 2021). However, most of these studies have examined the association with baseline hematological inflammatory markers. A longitudinal study found that changes in SII also influence the change in depressive symptoms (Mazza et al., 2021).

It is crucial to examine psychological factors while examining the association of inflammation and psychiatric disorder, as inflammation may represent the severity of the condition, influencing adaption and reaction towards the disease. Thus indirectly affecting psychiatric morbidity.

The findings are significant as we have examined both new onset psychiatric symptoms and clinical diagnosis; still, it should be viewed with limitations like the small and convenient sample (patients with less severe illnesses and possibly with higher health anxiety).

To conclude, the findings highlight that possibly inflammation is not a significant contributor to psychiatric morbidity in patients with COVID-19 in the long term, and factors like illness perception and psychosocial factors should be examined.

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Conflict of interest

None.

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References

- Ahmed, G.K., Khedr, E.M., Hamad, D.A., Meshref, T.S., Hashem, M.M., Aly, M.M., 2021. Long term impact of Covid-19 infection on sleep and mental health: a cross-sectional study. *Psychiatry Res.* 305, 114243 <https://doi.org/10.1016/j.psychres.2021.114243>.
- Banerjee, D., Viswanath, B., 2020. Neuropsychiatric manifestations of COVID-19 and possible pathogenic mechanisms: insights from other coronaviruses. *Asian J. Psychiatry* 54, 102350. <https://doi.org/10.1016/j.ajp.2020.102350>.

- Damiano, R.F., Caruso, M., Cincoto, A.V., de Almeida Rocca, C.C., de Pádua Serafim, A., Bacchi, P., Guedes, B.F., Brunoni, A.R., Pan, P.M., Nitri, R., Beach, S., Fricchione, G., Busatto, G., Miguel, E.C., Forlenza, O.V., HCFMUSP COVID-19 Study Group, 2022. Post-COVID-19 psychiatric and cognitive morbidity: preliminary findings from a Brazilian cohort study. *Gen. Hosp. Psychiatry* 75, 38–45. <https://doi.org/10.1016/j.genhosppsy.2022.01.002>.
- Huarcaya-Victoria, J., Barreto, J., Aire, L., Podestá, A., Caqui, M., Guija-Igreda, R., Castillo, C., Alarcon-Ruiz, C.A., 2021. Mental health in COVID-2019 survivors from a general hospital in Peru: sociodemographic, clinical, and inflammatory variable associations. *Int. J. Ment. Health Addiction* 1–22. <https://doi.org/10.1007/s11469-021-00659-z>.
- Lovibond, S.H., Lovibond, P.F., 1995. *Manual for the Depression Anxiety Stress Scales*, second ed., Psychology Foundation, Sydney.
- Magnúsdóttir, I., Lovik, A., Unnarsdóttir, A.B., McCartney, D., Ask, H., Kóiv, K., Christoffersen, L., Johnson, S.U., Hauksdóttir, A., Fawns-Ritchie, C., Helenius, D., González-Hijón, J., Lu, L., Ebrahimi, O.V., Hoffart, A., Porteous, D.J., Fang, F., Jakobsdóttir, J., Lehto, K., Andreassen, O.A., COVIDMENT Collaboration, 2022. Acute COVID-19 severity and mental health morbidity trajectories in patient populations of six nations: an observational study. *Lancet Public Health* 7 (5), e406–e416. [https://doi.org/10.1016/S2468-2667\(22\)00042-1](https://doi.org/10.1016/S2468-2667(22)00042-1).
- Mazza, M.G., Palladini, M., De Lorenzo, R., Magnaghi, C., Poletti, S., Furlan, R., Ciceri, F., COVID-19 BioB Outpatient Clinic Study group, Rovere-Querini, P., Benedetti, F., 2021. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. *Brain Behav. Immun.* 94, 138–147. <https://doi.org/10.1016/j.bbi.2021.02.021>.
- Ministry of Health and Family Welfare, Government of India 2020, Clinical Management Protocol: COVID-19. <https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf>. (Accessed 26 July 2022).
- Taquet, M., Luciano, S., Geddes, J.R., Harrison, P.J., 2021. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry* 8 (2), 130–140. [https://doi.org/10.1016/S2215-0366\(20\)30462-4](https://doi.org/10.1016/S2215-0366(20)30462-4).
- Yuan, N., Chen, Y., Xia, Y., Dai, J., Liu, C., 2019. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Transl. Psychiatry* 9 (1), 233. <https://doi.org/10.1038/s41398-019-0570-y>.

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