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COVID-19

Predictors of "brain fog" 1 year after COVID-19 disease

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Abstract

Introduction Brain fog has been described up to 1 year after SARS-CoV-2 infection, notwithstanding the underlying mechanisms are still poorly investigated. In this study, we aimed to evaluate the prevalence of cognitive complaints at 1-year follow-up and to identify the factors related to persistent brain fog in COVID-19 patients.

Methods Out of 246 COVID patients, hospitalized from March 1st to May 31st, a sample of 137 patients accepted to be evaluated at 1 year from discharge, through a full clinical, neurological, and psychological examination, including the Montreal Cognitive Assessment (MoCA), impact of event scale-revised (IES-R), Zung self-rating depression scale (SDS), Zung self-rating anxiety scale (SAS), and fatigue severity scale (FSS). Subjects with prior cognitive impairment and/or psychiatric disorders were excluded.

Results Patients with cognitive disorders exhibited lower MoCA score (22.9 ± 4.3 vs. 26.3 ± 3.1, $p = 0.002$) and higher IES-R score (33.7 ± 18.5 vs. 26.4 ± 16.3, $p = 0.050$), SDS score (40.9 ± 6.5 vs. 35.5 ± 8.6, $p = 0.004$), and fatigue severity scale score (33.6 ± 16.1 vs. 23.7 ± 12.5, $p = 0.001$), compared to patients without cognitive complaints. Logistic regression showed a significant correlation between brain fog and the self-rating depression scale values ($p = 0.020$), adjusted for age ($p = 0.445$), sex ($p = 0.178$), premorbid Cumulative Illness Rating Scale (CIRS) ($p = 0.288$), COVID-19 severity (BCRSS) ($p = 0.964$), education level ($p = 0.784$) and MoCA score ($p = 0.909$).

Conclusions Our study showed depression as the strongest predictor of persistent brain fog, adjusting for demographic and clinical variables. Wider longitudinal studies are warranted to better explain cognitive difficulties after COVID-19.

Keywords COVID-19 · Brain fog · Cognitive difficulties · Long COVID · Neurology

Cognitive symptoms have been commonly reported in post-COVID syndrome up to 1 year after the SARS-CoV-2 infection, together with anxiety, fatigue, myalgia, and chest tightness [1–3].

According to previous studies, cognitive complaints are commonly described as "brain fog," characterized by low-thinking, difficulties in focusing the attention, subjective confusion, and forgetfulness.

Recently, several imaging reports also showed brain functional changes in small series of patients presenting long-term cognitive symptoms after SARS-CoV-2 infection [4, 5]. Despite the growing literature in the field, the long-term course of cognitive deficits, their association with severity of the COVID-19 at onset, with premorbid conditions, and with other long-term symptoms is still the theme of debate—as the underlying mechanisms of cognitive deficits reported are largely unexplained [6, 7].

In this study, we aimed to evaluate the prevalence and predictive factors of cognitive complaints (CC) reported at 1-year follow-up in patients hospitalized for COVID-19 (Table 1).

Out of 246 patients admitted at the COVID-19 Unit, ASST Spedali Civili Hospital, Brescia (Italy), for respiratory complications of SARS-CoV-2 infection, from March 1st to May 31st, a sample of 132 patients was evaluated after 12 months from discharge. A full clinical, neurological, and

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Table 1 Demographic and clinical factors associated with subjective cognitive complaints. *p values were calculated by Mann Whitney test or Fisher's exact test, as appropriate. Abbreviations: BCRSS, Brescia-COVID Respiratory Severity Scale, CIRS, cumulative illness rating scale mRS, modified ranking scale; qSOFA, quick Sequential Organ Failure Assessment, IES-R, Impact of Event Scale-Revised; SDS, Self-rating depression scale; SAS, Self-Rating Anxiety Scale

	Patients without SCC (n = 107)	Patients with SCC (n = 25)	*p* value
Demographic and clinical characteristics			
Age, years	64.6 ± 12.4	68.5 ± 11.1	0.157
Sex, female	32 (30.2%)	7 (29.2%)	00.921
mRS pre	0.31 ± 0.6	0.39 ± 0.5	0.587
CIRS severity index pre-hospitalization	1.3 ± 0.3	1.3 ± 0.4	0.571
NHS at admission (median value)	5.8 ± 2.6	6.7 ± 2.5	0.121
qSOFA at admission	1.05 ± 1.3	1.88 ± 1.9	0.118
BCRSS at admission (median value)	0.5 ± 0.6	0.4 ± 0.5	0.473
Low-flow oxygen treatment	52 (49.5%)	15 (62.5%)	0.268
Non-invasive ventilation	9 (8.5%)	4 (16.7%)	0.258
Total days of O2 therapy	5.3 ± 8.6	6.9 ± 5.9	0.383
MoCA score at 6 M follow-up	25.4 ± 3.1	21.8 ± 3.1	< 0.001
MoCA score at 12 M follow-up	26.3 ± 3.1	22.9 ± 4.3	0.002
IES-R	26.4 ± 16.3	33.7 ± 18.5	0.050
Fatigue severity scale	23.7 ± 12.5	33.6 ± 16.1	0.001
SDS (Zung)	35.5 ± 8.6	40.9 ± 6.5	0.004
SAS (Zung)	36.5 ± 5.9	35.9 ± 7.7	0.674

psychological examination was performed, including the Montreal Cognitive Assessment (MoCA), impact of event scale-revised (IES-R), Zung self-rating depression scale (SDS), Zung self-rating anxiety scale (SAS), and fatigue severity scale (FSS).

Patients with premorbid dementia or cognitive impairment ($n = 2$) and depressive anamnestic syndrome ($n = 3$) were excluded.

Out of the total sample, 25 subjects (22%) reported CC consistent with brain fog, at 1-year follow-up.

Patients with and without CC did not differ for age, premorbid conditions, and severity of COVID-19 at onset, whereas CC subjects exhibited lower MoCA score (22.9 + 4.3 vs. 26.3 + 3.1, $p = 0.002$), higher IES-R score (33.7 + 18.5 vs. 26.4 + 16.3, $p = 0.050$), worse SDS score (40.9 + 6.5 vs. 35.5 + 8.6, $p = 0.004$), and higher Fatigue Severity Scale (FSS 33.6 + 16.1 vs. 23.7 + 12.5, $p = 0.001$). To explore factors associated with "brain fog," logistic regression model was carried out, controlling for multiple covariates.

Notably, depressive symptoms measured by SDS ($p = 0.02$; Exp(B) 1.09, 95% C.I. 1.01–1.18) emerged as the factor with strongest correlation with cognitive complaints, controlling for age ($p = 0.445$; Exp(B) 1.03, 95% C.I. 0.96–1.10), sex ($p = 0.178$; Exp(B) 0.40, 95% C.I. 0.11–1.51), premorbid Cumulative Illness Rating Scale (CIRS) ($p = 0.288$; Exp(B) 4.33, 95% C.I. 0.29–64.6), COVID-19 severity (BCRSS)($p = 0.964$; Exp(B) 0.98, 95% C.I. 0.41–2.32), education level ($p = 0.784$; Exp(B) 0.98, 95% C.I. 0.86–1.12), and MoCA score ($p = 0.909$; Exp(B) 0.99, 95% C.I. 0.80–1.22).

These findings confirmed that a relevant percentage of COVID-19 patients are still affected by "brain fog" associated with other post-COVID symptoms at 1-year follow-up, in line with larger previous surveys [6]. Moreover, brain fog subjects exhibited cognitive disturbances, albeit with preserved basic and instrumental daily living activities functions. Although the mechanisms underlying long-term cognitive involvement are still unclear, depressive symptoms emerged as the most important clinical variable associated with CC, regardless of MoCA performance. The results are of novel interest, especially when considering the exclusion of patients with premorbid cognitive or psychiatric disturbances. On one hand, the results of cognitive testing excluded the presence of severe cognitive deficits with impact in all-day life and possibly suggest that "brain fog" might be due to a depressive state. On the other, it has been claimed that depression might conversely refer to an inflammatory-mediated long-term brain dysfunction [8]. The lack of association we found between "brain fog" and COVID-19 severity suggests that factors other than infection have a prominent role for post-COVID sequelae. This fits with recent findings on psychosocial factors linked to premorbid brain-health vulnerability [9, 10]. A larger use of prospective neuronal and glial markers in post-COVID follow-up might allow a better understanding of factors leading to cognitive symptoms' progression or remission after the acute phases of the disease.

Despite some main limitations of this work, namely the unavailability of premorbid cognitive screening and the small sample size, this is the first longitudinal study to show a correlation between cognitive and depressive symptoms

after 1 year from COVID-19 recovery, independently from premorbid conditions and SARS-CoV-2 infection severity.

Larger longitudinal studies are warranted to shed further light on possible underlying mechanisms and future therapeutic strategies to reduce the burden of long-term neurological sequelae.

Declarations

Ethical approval The study received approval from local ethics committee of the ASST Spedali Civili Hospital, Brescia (NP 4067, approved 08.05. 2020).

Conflict of interest The authors declare no competing interests.

References

1. Zhang X, Wang F, Shen Y et al (2021) Symptoms and health outcomes among survivors of COVID-19 infection 1 year after discharge from hospitals in Wuhan. China JAMA Netw Open 4:e2127403
2. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ (2021) 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 8:416–427
3. Pilotto A, Cristillo V, Cotti Piccinelli S et al (2021) Long-term neurological manifestations of COVID-19: prevalence and predictive factors. Neurol Sci 42:4903–4907
4. Sollini M, Morbelli S, Ciccarelli M et al (2021) Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. Eur J Nucl Med Mol Imaging 48:3187–3197
5. Hugon J, Msika EF, Queneau M, Farid K, Paquet C (2022) Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. J Neurol 269:44–46
6. Hampshire A, Trender W, Chamberlain SR et al (2021) Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine 39:101044
7. Cristillo V, Pilotto A, Cotti Piccinelli S et al (2021) Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID-19 infection. J Am Geriatr Soc 69:2778–2780
8. Pilotto A, Masciocchi S, Volonghi I et al (2021) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) encephalitis is a cytokine release syndrome: evidences from cerebrospinal fluid analyses. Clin Infect Dis 73:e3019–e3026
9. Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE (2007) The effects of stress and stress hormones on human cognition: implications for the field of brain and cognition. Brain Cogn 65:209–237
10. Fiorenzato E, Zabberoni S, Costa A, Cona G (2021) Cognitive and mental health changes and their vulnerability factors related to COVID-19 lockdown in Italy. PLoS ONE 16:e0246204