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Psychiatric symptoms subsequent to COVID-19 and their association with clinical features: A retrospective investigation

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ABSTRACT

This study explores the association between psychiatric symptoms following COVID-19 and demographic, disease-related and premorbid clinical confounders. Global cognition, depression, anxiety and PTSD features were assessed in 152 post-COVID-19 patients, subdivided into being at risk for brain disorders or not. In both groups, clinically meaningful depression, anxiety and PTSD symptoms were mildly-to-moderately frequent (4−45%). No demographic or clinical variables predicted psychiatric measures (except for lower age predicting higher anxiety levels). Depression, anxiety and PTSD measures were associated among each other. Hence, depression-, anxiety- and PTSD-*spectrum* disturbances in COVID-19 survivors are likely to be unassociated with disease-related and premorbid features.

Introduction

SARS-CoV-2 infection has been acknowledged to possibly affect cognition and behavior due to both its neurotropic properties and systemic neuroinflammatory processes, as well as due to iatrogenic effects of COVID-19 treatments (*e.g.*, steroids and O_2 therapy) (Aiello et al., 2022a; 2022c; Manera et al., 2022; Pistarini et al., 2021). Psychiatric sequelae of COVID-19 have been also highlighted (Putri et al., 2021; Vanderlind et al., 2021), the most frequently detected being anxiety, depression and PTSD features. Screening for such disturbances has been thus suggested in this population (Pistarini et al., 2021), in the light of their negative influence on both prognosis and functional outcomes (Ptacek et al., 2020).

However, it is currently debated whether the determinants of psychiatric aftermaths in post-COVID-19 individuals are properly organic (*i.e.*, due to encephalopathic features) or psychogenic (*i.e.*, event-related and thus reactive) (Putri et al., 2021; Vanderlind et al., 2021). Moreover, the interplay between psychiatric sequelae of COVID-19 and both background (*i.e.*, demographic features and premorbid status) and disease-related variables (*e.g.*, clinical phenotype, treatment-related features, etc.) are poorly understood (Mazza et al., 2020; Liu et al., 2021).

This study thus aimed at: (1) exploring the etiology of psychiatric sequelae of SARS-CoV-2 infection by assessing their association with both cognitive and clinical confounders; (2) further investigating the interplay between such disturbances and both background/premorbid and disease-related features.

Methods

Participants

Data from $N = 152$ COVID-19-recovered inpatients referred to Istituti Clinici Scientifici Maugeri (Northern Italy) between May 2020 and 2021 were retrospectively collected.

Disease severity was classified as “asymptomatic”, “mildly

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symptomatic", "mild-to-moderate" (requiring O_2 but not ventilation) and "moderate-to-severe" (requiring either non-invasive ventilation or ICU).

According to Manera et al. (2022) and Aiello et al. (2022a, 2022b, 2022d), patients were classified, based on remote/recent/COVID-19-related medical records, into being already at risk or not for cognitive/behavioural dysfunctions (Neuro+ *vs.* Neuro-). Neuro+ groups included patients with: (1) previous neurological (*e.g.*, neurodegenerative diseases, stroke or brain neoplasms) and psychiatric diagnoses (*e.g.*, anxiety, mood or psychotic disorders); (2) previous severe internal conditions (*e.g.*, system/organ failures and cardiovascular events) or ≥3 internal/metabolic factors that are acknowledged to possibly affecting cognition/behavior (*i.e.*, hypertension, diabetes, or thyroidal dysfunctions) (Armstrong and Morrow, 2010); (3) COVID-19-related cognitive/behavioural manifestations (*e.g.*, delirium). Neuro- patients did not present such premorbid/COVID-19-related features. Two independent raters performed Neuro± classification blinded to patients' outcomes. Disagreements were solved *via* discussion with a third independent rater.

Materials

Patients underwent depression (Patient Health Questionnaire-9, PHQ-9) (Kroenke et al., 2001), anxiety (Generalized Anxiety Disorder-7, GAD-7) (Spitzer et al., 2006), PTSD (Impact Event Scale-Revised, IES-R) [Pierantonio et al., 2003] and cognitive (Mini--Mental State Examination, MMSE; Montreal Cognitive Assessment, MoCA) (Carpinelli-Mazzi et al., 2020; Aiello et al., 2022c) assessment.

Statistics

MMSE and MoCA scores were adjusted for age and education and compared to respective cut-offs based on current norms (Carpinelli--Mazzi et al., 2020; Aiello et al., 2022c). PHQ-9, GAD-7 and IES-R scores were classified according proposed thresholds (PHQ-9: "absent" if ≤4, "sub-clinical" if >5 and ≤9, "mild" if >10 and ≤14, "moderate" >15 and ≤19, "severe" if ≥20; GAD-7: "absent" if ≤4, "mild" if >5 and ≤9, "moderate" if >10 and ≤14, "severe" if >15; IES-R: "present" if ≥33) (Kroenke et al., 2001; Pietrantonio et al., 2003; Spitzer et al., 2006). Herewith, "moderate" and "severe" classifications for both the PHQ-9 and GAD-7 were addressed as clinically meaningful.

Continuous measures were normally distributed as indexed by skewness and kurtosis values (all $<|1|$ and $|3|$, respectively) (Kim, 2013). Accordingly, linear model analyses were run.

First, to test whether demographic, premorbid, disease-related and cognitive measures accounted for depression, anxiety and PTSD features, three multiple linear regression models were run by separately addressing, as outcomes, PHQ-9, GAD-7 and IES-R scores, by entering as predictors age, education, sex, Neuro ± classification, disease severity, ICU admission, steroidal treatment, co-morbid infection during COVID-19, disease duration, time from onset symptoms to evaluation and MMSE scores.

Second, to test the association among depression, anxiety and PTSD features, partial correlation analyses were run between PHQ-9, GAD-7 and IES-R by partialling out the same set of variables addressed as predictors within the above regression models.

Bonferroni's correction were applied both when selecting significant predictors within the regression models (*i.e.*, $\alpha_{adjusted}$=0.05/number of predictors) and within the partial correlation analyses (*i.e.*, $\alpha_{adjusted}$=0.05/number of comparisons). Analyses were performed *via* jamovi 2.3 (the jamovi project, 2022). Missing data were excluded pairwise.

Results

Background, clinical, cognitive and psychiatric features of patients are displayed in Table 1. Neuro- and Neuro+ patients were not balanced for age (p=.042), sex (p<.001), disease severity (p<.001), ICU admission (p<.001) and infection (p=.022) rates, as well as cognition (MMSE: p=.005; MoCA: p=.035) (Table 1).

Table 1
Participants' background, clinical and psychometric measures.

Domain	Outcome	Neuro+	Neuro-	$p^{\dagger}$
Background				
	N	103	49	–
	Age (years)	68.46±13.73 (18–93)	63.82±11.46 (28–85)	.042*
	Sex (male/female)	43/6	58/45	>0.001*
	Education (years)	10.31±3.87 (2–19)	11.08 ± 3.92 (3–18)	.254
Clinical				
	Disease duration (days)	43.46±25.31 (2–113)	43.17±26.66 (5–129)	.951
	Time from onset (days)	88.31±76.11 (7–422)	74.75±32.44 (26–186)	.804
	Severity			<0.001*
	Asymptomatic	11.7%	2%	–
	Mildly symptomatic	19.4%	6.1%	–
	Mild-to-moderate	31.1%	12.2%	–
	Moderate-to-severe	37.9%	79.6%	–
	ICU	38.8%	69.4%	.001*
	Steroids	34.2%	50%	.228
	Infection	25.2%	43.8%	.025*
Psychometric				
	MMSE (*N* = 152)	26.92±3.40 (15–30)	28.18±2.06 (22–30)	.005*
	MoCA (*N* = 97)	21.72±4.98 (8–30)	23.50±3.13 (18–30)	.035*
	PHQ-9 (*N* = 149)	5.62±3.92 (0–17)	6.21±4.82 (0–21)	.432
	Absent	45.5%	43.8%	
	Sub-clinical	40.6%	31.3%	
	Mild	9.9%	18.8%	
	Moderate	4%	4.2%	
	Severe	–	2.1%	
	GAD-7 (*N* = 128)	5.08±4.2 (0–16)	5.33±4.75 (0–17)	.769
	Absent	58%	52.5%	
	Mild	22.7%	27.5%	
	Moderate	17%	15%	
	Severe	2.3%	5%	
	IES-R (*N* = 42)	24.41±22.21 (0–68)	29.4 ± 20.75 (0–68)	.457
	Absent	63.6%	55%	
	Present	36.4%	45%	

Notes. Neuro+=patients already at risk for cognitive/behavioural dysfunctions; Neuro-=patients not already at risk for cognitive/behavioural dysfunctions; ICU=intensive care unit; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; PHQ-9=Patient Health Questionnaire-9; GAD-7=Generalized Anxiety Disorder-7; IES-*R*=Impact Event Scale-Revised.
† p-values refer to either χ^2 (categorical measures) or independent sample t/F or Mann-Whitney U (continuous measures).
* significant at α=0.05 or less.

As to the PHQ-8 and GAD-7, a moderately high cumulative prevalence of abnormal, clinically meaningful scores (*i.e.*, ranging from "moderate" to "severe") was detected in both groups (PHQ-9: Neuro+: 4%; Neuro-: 6.3%; GAD-7: Neuro+: 19.3%; Neuro-: 20%). Similar results yielded as to the IES-R (above-cut-off scores: Neuro+: 36.4%; Neuro-: 45%).

At $\alpha_{adjusted}$=0.005, no variables significantly predicted the PHQ-9 (p≥.072) and the IES-R (p≥.08), whereas GAD-7 scores were negatively predicted by age only (β=−0.41; t(68)=−3.2; p=.002).

At $\alpha_{adjusted}$=0.02, significant associations were detected between PHQ-9 and both GAD-7 scores (r(82)=0.71; p<.001) and IES-R scores (r

(37)=0.78; $p<.001$), whereas not between the GAD-7 and IES-R ($p=.054$).

Discussion

This study replicates previous findings reporting the occurrence of psychiatric features within the depression-, anxiety- and PTSD-*spectrum* in post-COVID-19 individuals (Vanderlind et al., 2021). However, the lack of associations between psychodiagnostic measures and cognition, premorbid risk factors for cognitive/behavioural dysfunctions and disease-related features suggests that these properly organic variables do not fully account for psychiatric symptoms in post-COVID-19 patients. This hypothesis would be supported by the fact that a number of psychodiagnostic measures were highly internally related: hence, event-related occurrences might determine a reactive psychopathological complex including depression, anxiety and PTSD symptoms. However, the observational nature of this investigation, as well as the fact that several other possible confounders have not been addressed (*e.g.*, stressors contextual to the pandemic, such as social restrictions; physical examinations), do not allow to draw definite inferences on the psychiatric *sequelae* of COVID-19.

As to the finding of lower age being associated with higher anxiety levels as assessed by the GAD-7, this is in line with previous evidence showing that younger COVID-19 patients might be at a higher risk for clinical anxiety when compared to older ones (Li et al., 2021).

The major limitations of this study are the adoption of short-lived instruments, the presence of missing values across different measures and a lack of follow-up evaluations. Future studies should aim at overcoming such issues. Moreover, it should be born in mind that the present Neuro± classification, despite having been adopted in previous studies by the present research group (Aiello et al., 2022a; 2022c; 2022d; Manera et al., 2022), suffers from subjectivity. Thereupon, further investigations are needed that aim at identifying a similar classification system that nonetheless is as less subjective as possible

Strengths of results herewith reported are, by contrast, a relatively high sample size and having taken into account the premorbid risk for cognitive/behavioural dysfunctions, thus increasing their the external validity.

Author contribution statement

conceptualization: E.F., D.P., E.N.A., M. R. M., M. O.; data collection: E. F., D. P., A. R., M. R. M., F. G., M. O.; statistical analyses: E. N. A.; drafting: E. F., D. P., E. N. A., A. R., M. R. M., M. O.; revision: E.F., D. P., E. N. A., A. R., M. R. M., F. G., M. O., C. P.; resources: E.F., D. P., M. R. M., F. G., M. O., C. P.

Declaration of Competing Interest

The Authors declare no known conflicts of interest.

Compliance with ethical standards

This study received approval by the local Ethics Committee (I.D.: 2470, 8 September 2020).

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