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Clinical features and cognitive sequelae in COVID-19: a retrospective study on N=152 patients

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Abstract:	Background. The novel human coronavirus (SARS-CoV-2) shows neurotropism and systemically affects the central nervous system (CNS). Cognitive deficits have been indeed reported as both short- and long-term sequelae of SARS-CoV-2 infection. However, the association between these disturbances and background/disease-related clinical features remain elusive. This work aimed at exploring how post-infective cognitive status relate to clinical/treatment outcomes by controlling for premorbid/current risk factors for cognitive deficits. Methods. Cognitive measures (Mini-Mental State Examination; MMSE) of N =152 COVID-19 patient were retrospectively assessed in relation to disease severity, intensive care unit (ICU) admission, steroidal treatment and occurrence of other viral/bacterial infections by controlling for remote/recent/COVID-19-related risk factors for cognitive deficits (at-risk vs. not-at-risk: Neuro+ vs. Neuro-). Results. Descriptively, impaired MMSE performances were highly prevalent in mild-to-moderate patients (26.3%). ICU-admitted patients made more errors (p =.021) on the MMSE than those not admitted when partialling out risk factors and age - the latter

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Abstract

Background. The novel human coronavirus (SARS-CoV-2) shows neurotropism and systemically affects the central nervous system (CNS). Cognitive deficits have been indeed reported as both short- and long-term sequelae of SARS-CoV-2 infection. However, the association between these disturbances and background/disease-related clinical features remain elusive. This work aimed at exploring how post-infective cognitive status relate to clinical/treatment outcomes by controlling for premorbid/current risk factors for cognitive deficits.

Methods. Cognitive measures (Mini-Mental State Examination; MMSE) of *N*=152 COVID-19 patient were retrospectively assessed in relation to disease severity, intensive care unit (ICU) admission, steroidal treatment and occurrence of other viral/bacterial infections by controlling for remote/recent/COVID-19-related risk factors for cognitive deficits (at-risk *vs.* not-at-risk: Neuro+ *vs.* Neuro-).

Results. Descriptively, impaired MMSE performances were highly prevalent in mild-to-moderate patients (26.3%). ICU-admitted patients made more errors (p=.021) on the MMSE than those not admitted when partialling out risk factors and age - the latter negatively influencing performances. When addressing Neuro- patients only, steroidal treatment appear to improve MMSE scores among those suffering from other infections (p=.025).

Discussion. Cognitive sequelae of COVID-19 are likely to arise from a complex interplay between background/clinical premorbid features and disease-related/interventional procedures and outcomes. Mild-to-moderate patients requiring assistive ventilation who however are not admitted to an ICU are more likely to suffer from cognitive deficits - despite their etiology remaining elusive.

Keywords: SARS-CoV-2; COVID-19; neuropsychology; ICU; steroid; premorbid.

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1. Introduction

Central nervous system (CNS) involvement has been acknowledged in patients infected with the novel human coronavirus (SARS-CoV-2) - due to both its neurotropic/neuroinvasive properties and inflammatory processes/secondary systemic disorders [Baig *et al.*, 2020; Zubair *et al.*, 2020].

Cognitive deficits within have been indeed reported and postulated as both short- and long-term sequelae of the disease caused by SARS-CoV-2 (COVID-19) [Rabinovitz *et al.*, 2020; Alnefeesi *et al.*, 2021; Pistarini *et al*., 2021].

Most studies suggested deficits in memory, executive functioning and attention [Alemanno *et al*., 2021; Helms *et al*., 2020; Pistarini *et al*., 2021; Wilson *et al*., 2020; Zhou *et al*., 2020]. Furthermore, results from previous pandemics of acute respiratory illness (*e.g*., middle-east respiratory syndrome) and existing knowledge of neurological outcomes in pulmonary disorders suggested that neuropsychological sequelae are to be expected in patients with COVID-19 [Bailey *et al*., 2021]. Coronavirus infections are indeed believed to increase and thereby extending the risk of post-infection cognitive dysfunction and accelerating neurodegenerative processes [Richie *et al*., 2020].

Pistarini *et al.* (2021) found a high prevalence of cognitive impairments in both COVID-19 and post-COVID-19 patients as assessed by a I-level, global cognition test (Montreal Cognitive Assessment). By contrast, a recent 4-month follow-up study [Mattioli *et al*., 2021] investigated cognitive impairments after SARS-CoV-2 infection in a group of mild–moderate post-COVID-19 patients and found no differences compared to non-COVID-19 cases.

It is thus currently debated whether cognitive impairment actually represent a SARS-CoV-2-specific complication or it is secondary to extra-CNS disorders – *e.g.*, systemic inflammation [Stracciari *et al.*, 2021].

Moreover, certain issues remain open as to the association between cognitive sequelae and both disease-related and background clinical variables. First, it is challenging to assess post-infective cognitive status by controlling for possibly intervening premorbid conditions/disease-related complications. Second, intensive care unit (ICU) admission has been reported to counterintuitively represent a protective factor towards cognitive outcomes [Alemanno *et al.*, 2021]. Moreover, the relation between cognitive dysfunctions and possible iatrogenic effects of steroidal treatment is still poorly understood [Ghasemiyeh *et al.*, 2020].

The present study thus aimed at investigating how cognitive outcomes relate to clinical/treatment features in COVID-19 patients by taking into account premorbid/disease-related clinical features possibly affecting cognition.

2. Methods

2.1 Materials

Data from *N*=152 post-infectious SARS-CoV-2 patients referred to either sub-acute or specialist rehabilitation units of Istituti Clinici Scientifici Maugeri located in Northern Italy, between May 2020 and May 2021 were retrospectively collected (see Table 1). The study was approved by the local Ethical Committee (Approval Number: 2470, 8 September 2020).

All patients had been administered the Mini-Mental State Examination (MMSE) [Measso *et al.*, 1993] - the most commonly used tool for screening cognitive impairment and consists of a brief (5-10') 30-point scale. The presence of cognitive impairment was defined by a total score <23.80 adjusted for age and education in the Italian population [Measso *et al.*, 1993]. .

Furthermore, information regarding neurological, psychiatric and general medical history were retrieved, along with data regarding the clinical manifestations of COVID-19. A classification according to disease severity was performed: asymptomatic; mildly symptomatic; mild-to-moderate: requiring O_2 therapy but not ventilation; moderate-to-severe: requiring either non-invasive ventilation or admitted to an ICU.

Furthermore, patients were sub-divided into those who had either remote, recent or COVID-19-related conditions possibly affecting cognitive functioning (Neuro+) and those who did not (Neuro-). Neuro+ group included patients with: a) neurological diseases (*e.g.*, Parkinson's disease, stroke); b) severe psychiatric disorders (*e.g.*, depression, post-traumatic stress-disorder); c) severe internal conditions (*e.g.*, atrial fibrillation); d) at least 3 risk factors for NPs impairment (*e.g.*, type-II diabetes, arterial hypertension and chronic obstructive pulmonary disease). This group however did not encompass patients that suffered from acute respiratory distress syndrome (ARDS)/respiratory insufficiency (requiring or not assistive ventilation) or were admitted to an ICU due to COVID-19. This expedient was implemented in order to rule out possible overlapping co-occurrences with the *ICU*/*Severity* factors. As to the inclusion criteria of Neuro-, they did not present with the aforementioned risk factors for cognitive decline.

Two independent Authors performed this categorization blinded to both each other's' decision and patients' psychometric outcomes; disagreements were solved by discussion with a third independent Author. According to this grouping, 103 patient were classified as Neuro+ and 49 as Neuro-.

-- Insert Table 1 about here --

2.3 Statistical analyses

Normality checks were performed by assessing skewness and kurtosis values [Kim, 2013].

According to data distribution, either linear or generalized linear models [Aiello *et al.*, 2020] were implemented for assessing predictions of interest. Associations between continuous variables were tested *via* either Pearson's or Spearman's coefficient.

Group (Neuro+ *vs.* Neuro-) was partialled out in each model in order to control for premorbid/disease-related confounders. As Neuro+ and Neuro- patients were comparable for education ($t(150)=.63$; $p=.366$) but not for age ($t(150)=-2.05$; $p=.042$; Neuro+: $M=68.5$, $SD=13.7$; Neuro-: $M=63.8$, $SD=11.5$), the latter was entered as a covariate within models including *Group*.

ICU (admitted *vs.* not admitted), *Steroids* (treated *vs.* not treated with steroids), *Infection* (occurrence *vs.* absence of a bacterial/viral infection during COVID-19), and *Severity* (mild - recoded by merging the first two original levels into one - *vs.* mild-to-moderate *vs.* moderate-to-severe) effects were tested on both the MMSE and its sub-scores. Domain-specific scales were defined as follows: spatial and temporal orientation (0-10); immediate and delayed recall (0-6); attention (0-5); language (0-8); constructional praxis (0-1). Within each implemented model, interactions between target (*e.g.*, *ICU*) and control (*i.e.*, *Group* and age) variables, as well as between control variables themselves, were not tested.

Bonferroni correction for multiple comparisons was applied if appropriate.

Analyses were performed via SPSS 27 [IBM Corp., 2020] and jamovi 1.6 [the jamovi project, 2020].

3. Results

Overall prevalence of cognitive deficits as assessed *via* the MMSE was 12.5%. Table 2 displays prevalence estimates sub-divided according to target factors. Below-cut-off MMSE

percentage was visibly higher in Neuro+ (16.5%) *vs.* Neuro- (4.1%) patients. Moreover, within severity degrees, impaired MMSE performances were notably more frequent for mild-to-moderate (26.3%). Finally, a trend towards a lower prevalence of defective MMSE scores was detected in ICU-admitted patients (19.2%) - when descriptively compared to those not admitted (5.4%).

When testing the association between MMSE scores and disease duration/time from onset to evaluation separately for the four severity sub-groups, no significant coefficients arose at $\alpha_{adjusted}$=.05/4=.013.

MMSE both total and sub-scores were heavily left-skewed and overdispersed. Therefore, predictions on the MMSE were initially run *via* Negative Binomial regressions, by addressing the number of errors (subtracting the score to its maximum achievable) as the outcome [Aiello *et al.*, 2020].

When individually testing target factors on MMSE total errors with *Group* and *Age* partialled out, a significant effect of *ICU* arose ($\chi^2(1)=5.3$; $p=.021$) - with ICU-admitted patients ($M=1.72$; $SE=.24$) making less errors than those not admitted ($M=2.73$; $SE=.38$); by contrast, neither *Severity* ($\chi^2(3)=2.07$; $p=.356$), nor *Steroids* ($\chi^2(1)=.49$; $p=.485$) nor *Infection* ($\chi^2(1)=.8$; $p=.372$) yielded significance. Notably, age negatively influenced the performance in all the above models ($p\leq.002$), whereas *Group* never showed significance ($.052\leq p\leq.28$). Consistent results were detected when building a model encompassing *ICU*, *Infection* and *Steroids* along with their interactions: *ICU* and age were predictive *per se* ($\chi^2(1)=5.5$; $p=.019$ and $\chi^2(1)=4.7$; $p=.029$, respectively), whereas no other main ($.395\leq p\leq.75$) or interactive ($.1\leq p\leq.93$) terms were significant.

As being the only significant target factor in previous models, *ICU* was further tested on MMSE Orientation, Attention, Memory and Language errors by controlling for *Group* and age. The same model was instead tested on constructional praxis *via* a logistic regression. *ICU* was not found to affect performances on any of the sub-scales ($.112\leq p\leq.311$). However, ICU admission predicted ($\chi^2(1)=4.4$; $p=.036$) a higher probability ($M=.88$; $SE=.04$) of responding correctly to constructional praxis item - when compared to non-admission ($M=.72$; $SE=.06$).

Factors of interest were then further tested on Neuro- patients' MMSE scores only ($N=49$) by controlling for age and education. As both normality ($W=.957$; $p=.38$) and homoscedasticity ($F(7,16)=1.5$; $p=.435$) assumptions for residuals were met, a linear model was run - which encompassed all possible between-factor interactions. No significant terms arose with the

exception of a two-way *Steroids*Infection* interaction ($F(1,14)=6.3$; $p=.025$; $\eta^2=.31$) - whose post-hoc, Bonferroni-corrected decomposition revealed that, among patients suffering from infections, those treated with steroids performed significantly ($t(14)=-3.86$; $p=.01$) better ($M=29.1$; $SE=.64$) than those not treated with steroids ($M=25.5$; $SE=.67$).

-- Insert Table 2 about here --

4. Discussion

This work sheds further light on the association between cognitive sequelae of SARS-CoV-2 infection and premorbid/disease-related clinical variables [Alnefeesi *et al.*, 2021].

With respect to the protective role of ICU admission on cognitive functions, the present results are in line with the report by Alemanno *et al.* (2021). It can thus be hypothesized that patients presenting with ARDS/respiratory insufficiency who underwent intensive cares might have suffered less from cerebral hypoxia than those treated with non-invasive ventilation [Alemanno *et al.*¸2021] - despite these treatments being more aggressive.

Furthermore, ICU admission being shown to affect global cognition but not specific instrumental domains further supports the notion that COVID-19-related cognitive deficits are likely to reflect a decrease in general cognitive efficiency - which is typical of critical illnesses also affecting the CNS [Jaywant *et al.*, 2021].

It is moreover worth mentioning that the trend towards a poorer cognitive outcome in mild-to-moderate patients when compared to both mild and moderate-to-severe ones also appears to mirror Alemanno *et al.*'s (2021) findings.

The present work does not provide overall conclusive evidence regarding the association between cognitive outcomes and steroidal treatment in COVID-19 patients [Ghasemiyeh *et al.*, 2020]. This might have been due to missing values as far as whether patients have been treated with steroids (information not available for $N=52$ patient).

However, when selectively assessing patients judged as not at risk for cognitive impairment, steroids appeared to improve cognitive outcomes when infections occurred during the disease course. Therefore, although steroidal interventions have been postulated as possibly iatrogenic on cerebral functions [Ghasemiyeh *et al.*, 2020], they might be beneficial to cognitive outcomes when other inflammatory processes co-occur with COVID-19.

As for background outcomes, findings here reported strongly supports the role of advanced age as a risk factor for a worse cognitive outcome in post-infective SARS-CoV-2 patients [Almeria *et al.*, 2020]. Moreover, although no strong inferential evidence emerged, a descriptive trend towards a higher prevalence of cognitive dysfunction in already-at-risk COVID-19-recovered patients could be noted [Almeria *et al.*¸2020].

A limitation of this report is represented by the fact that only the MMSE has been addressed as a cognitive measure, this possibly leading to an underestimation of the prevalence of COVID-19-related cognitive aftermaths. Indeed, it has been suggested that other screeners, such as the Montreal Cognitive Assesssment (MoCA) [Aiello *et al.*, 2021b] and the Frontal Assessment Battery [Aiello *et al.*, 2021a], may be more appropriate for detecting such dysfunctions – possibly due to the an higher sensitivity [Aiello *et al.*, 2021c; Beaud *et al.*, 2021].

In conclusion, cognitive sequelae of COVID-19 are likely to arise from a complex interplay between background/clinical premorbid features and disease-related/interventional procedures and outcomes. Mild-to-moderate patients requiring assistive ventilation who however are not admitted to an ICU are more likely to suffer from cognitive deficits - despite their etiology remaining elusive. Further investigations are thus needed, also focusing on the longitudinal interplay of cognition and clinical features [Blazhenets *et al.*, 2021].

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Table 1. Participants' background, clinical and psychometric measures.

Domain	Outcome			
Background				
	N		152	
	Age (years)		67±13.2 (18-93)	
	Sex (male/female)		101/51	
	Education (years)		10.6±3.9 (2-19)	
Clinical				
	Disease duration (days)		43.4±25.6 (2-129)	
	Time from onset (days)		84±65.6 (7-422)	
Severity	Asymptomatic		8.6%	
	Mildly symptomatic		15.1%	
	Mild-to-moderate		25%	
	Moderate-to-severe		51.3%	
	ICU		48.7%	
	Steroids		38%	
	Infection		31.1%	
Comorbidities				
		Remote	**Recent**	**COVID-19-related**
	Neurological	30.6%	15.1%	28.9%
	Psychiatric	33.3%	5.9%	3.3%
	Cardiac	59.2%	3.3%	7.9%
	Pulmonary	12.9%	2%	19.1%
	Infective	5.4%	.7%	5.9%
	Metabolic	23.1%	-	2%
Psychometric				
MMSE	Total		27.3±3.1 (15-30)	
	Temporal orientation		4.5±.9 (1-5)	
	Spatial orientation		4.6±.7 (2-5)	
	Immediate recall		3±.2 (1-3)	
	Attention		4.4±1.3 (0-5)	
	Delayed recall		2.3±.9 (0-3)	
	Language		7.8±.6 (4-9)	
	Constructional praxis		.8±.4 (0-1)	

Notes. MMSE=Mini-Mental State Examination; ICU=intensive care unit; COVID-19=coronavirus disease 2019.

Table 2. Below cut-off scores on the MMSE according to disease-related variable.

		<23.8†
Severity		
	Asymptomatic	7.7%
	Mildly symptomatic	13%
	Mild-to-moderate	26.3%
	Moderate-to-severe	6.4%
	Neuro+	16.5%
	Neuro-	4.1%
ICU	Admitted	5.4%
	Not admitted	19.2%
Steroids	Yes	13.2%
	No	12.9%
Infections	Yes	8.5%
	No	14.4%

Notes. MMSE=Mini-Mental State Examination; Neuro+/-=patients with/without remote/recent/disease-related comorbities possibly affecting cognition. †=cut-off from Measso *et al.* (1993).