Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short communication

Association of depression and COVID-induced PTSD with cognitive symptoms after COVID-19 illness

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ABSTRACT

Objective: Many patients recovering from COVID-19 report persistent psychological and cognitive symptoms months after viral clearance. We examined the association of depression and COVID-induced PTSD with cognitive symptoms following COVID-19 illness.

Methods: Patients treated for COVID-19 between March 26 and May 27, 2020 were surveyed three months later. Cognitive symptoms were assessed by asking "Since your COVID-19 illness, do you now have more difficulty: 1) Remembering conversations a few days later? 2) Remembering where you placed familiar objects? 3) Finding the right words while speaking?" Patients endorsing at least one such complaint were coded positive for cognitive symptoms. Logistic regression was used to estimate the association of depression (PHQ-8 $\geq$ 10) and COVID-induced PTSD (PCL-5 $\geq$ 30) with cognitive symptoms, adjusting for demographic and clinical factors.

Results: Among 153 participants, 44.4% reported at least one cognitive symptom, 18.3% were depressed, and 23.5% had COVID-induced PTSD. Adjusting for covariates, depression (OR 5.15, 95% CI 1.30–20.35, $p = 0.02$) and COVID-induced PTSD (OR 3.67, 95% CI 1.13–11.89, $p = 0.03$) were significantly associated with cognitive symptoms; self-reported history of mental illness was also associated (OR 4.90, 95% CI 1.24–19.41, $p = 0.02$).

Conclusions: Depression, COVID-induced PTSD, and prior mental illness were strongly associated with cognitive symptoms three months after acute COVID-19 illness.

1. Introduction

Although Coronavirus Disease 2019 (COVID-19) primarily affects the respiratory system, neurological manifestations are also common. Patients with severe COVID-19 can develop encephalitis, vasculitis, and cerebrovascular disease [1,2], often leading to persistent neurocognitive and neuropsychiatric problems [3–5]. Even mild-to-moderate infections may impair memory, attention, and concentration for months [6–9]. The pathogenesis of this so-called "COVID brain fog" [6,8,9] remains unclear, but may be related to psychological distress following COVID-19 illness [3]. Accordingly, we examined the association of current depression and COVID-induced posttraumatic stress disorder (PTSD) with cognitive symptoms in patients recovering from COVID-19.

2. Methods

Patients treated for COVID-19 at Columbia University Irving Medical Center (CUIMC), either in the emergency department (ED) or inpatient wards, and discharged between March 26 and May 27, 2020 were enrolled. Participants were recruited from a registry of COVID-19 patients referred to a post-discharge remote monitoring program [10]. Approximately three months later, patients were surveyed about the physical, psychological, and neurocognitive impact of their COVID-19 illness. Eligibility requirements included age $\geq$ 18 years, English or Spanish fluency, discharge home, and confirmed COVID-19 infection. Patients with severe cognitive impairment precluding completion of the study protocol were excluded. Surveys could be completed in English or Spanish via telephone or online. Enrollment and data collection were conducted by bilingual staff, and Spanish versions of study instruments

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were professionally translated. The CUIMC Institutional Review Board approved the study, and all patients provided verbal informed consent.

The survey included three questions based on the Cognitive Change Index [11]: "Since your COVID-19 illness, do you now have more difficulty: 1) Remembering conversations a few days later? 2) Remembering where you placed familiar objects? 3) Finding the right words while speaking?" Patients endorsing at least one such complaint were coded positive for cognitive symptoms. COVID-induced PTSD was assessed using the PTSD Checklist for DSM-5 cued to the COVID-19 illness (PCL-5, ≥30 positive) [12]. Current depression was assessed using the 8-item Patient Health Questionnaire (PHQ-8, ≥10 positive) [13]. Self-reported demographics (age, sex, race, ethnicity, employment status), self-reported history of mental illness (depression, anxiety, PTSD), and chart-extracted clinical variables (length of hospitalization, level of care, intubation status) were used as covariates in regression modeling.

Characteristics of patients with versus without cognitive symptoms were compared using descriptive statistics. Logistic regression was used to estimate the association of current depression and COVID-induced PTSD with cognitive symptoms, adjusting for covariates selected a priori based on literature review. Analyses were conducted using SAS statistical software (v9.4, SAS Institute) at a two-sided alpha of 0.05.

3. Results

Among 930 eligible patients, 510 were contacted, 255 consented, and 153 completed the survey. Surveys were conducted a median 3.68 (IQR 2.60–5.70) months post-discharge, 58 by telephone and 95 online. Mean age was 54.5 ± 16.7 years, 39.9% female, 17.0% White, 15.0% Black, and 54.9% Hispanic. Mean length of hospitalization was 8.0 ± 8.1 days, with 18.3% of patients treated in the ED, 81.7% admitted to the inpatient wards, 5.9% admitted to the ICU and 4.6% requiring intubation (Table 1). Overall, 44.4% of patients endorsed at least one cognitive symptom (24.2% forgot conversations, 34.6% misplaced items, 28.1% had word-finding difficulty). Prior mental illness was reported by 15.0% of patients (13.1% depression, 8.5% anxiety, 2.6% PTSD), current depression by 18.3%, and COVID-induced PTSD by 23.5%.

In unadjusted logistic models, female sex (OR 2.12, 95% CI 1.08–4.16, $p = 0.03$), prior mental illness (OR 4.62, 95% CI 1.70–12.56, $p < 0.01$), current depression (OR 5.09, 95% CI 2.01–12.89, $p < 0.01$), and COVID-induced PTSD (OR 4.88, 95% CI 2.14–11.11, $p < 0.01$) were each associated with cognitive symptoms. In the fully-adjusted model, prior mental illness (OR 4.90, 95% CI 1.24–19.41, $p = 0.02$), current depression (OR 5.15, 95% CI 1.30–20.35, $p = 0.02$), and COVID-induced PTSD (OR 3.67, 95% CI 1.13–11.89, $p = 0.03$) remained significant (Table 2). In a sensitivity analysis excluding ICU patients, these associations became modestly attenuated but the overall pattern remained unchanged.

Table 1
Participant characteristics stratified by cognitive symptom status three months after COVID-19 illness ($n = 153$).

Characteristic	All (n = 153)	Cognitive symptoms present ($n = 68$, 44.4%)	Cognitive symptoms absent ($n = 85$, 55.6%)	*P* value
Age, years (mean ± SD)	54.5 ± 16.7	58.0 ± 15.9	52.2 ± 16.9	0.07
Sex[a]				
Male	84 (54.9%)	30 (47.6%)	54 (65.9%)	0.03
Female	61 (39.9%)	33 (52.4%)	28 (34.2%)	
Race/Ethnicity[b]				
Non-Hispanic White	26 (17.0%)	11 (16.2%)	15 (17.7%)	0.81
Non-Hispanic Black	23 (15.0%)	12 (17.7%)	11 (12.9%)	0.42
Hispanic	84 (54.9%)	35 (51.5%)	49 (57.7%)	0.45
Employment status				
Employed	94 (61.4%)	41 (60.3%)	53 (62.4%)	0.79
Unemployed	59 (38.6%)	27 (39.7%)	32 (37.7%)	
Prior mental illness[c]				
Yes	23 (15.0%)	17 (27.0%)	6 (7.4%)	<0.01
No	121 (79.1%)	46 (73.0%)	75 (92.6%)	
Treatment location				
Emergency department	28 (18.3%)	16 (23.5%)	12 (14.1%)	0.13
Inpatient ward	125 (81.7)	52 (76.5%)	73 (85.9%)	
Highest level of inpatient care				
Intensive care unit	9 (5.9%)	3 (4.4%)	6 (7.1%)	0.73[f]
Regular hospital floor	144 (94.1%)	65 (95.6%)	79 (92.9%)	
Intubated during hospitalization				
Yes	7 (4.6%)	3 (4.4%)	4 (4.7%)	1.00[f]
No	146 (95.4%)	65 (95.6%)	81 (95.3%)	
Length of hospitalization, days (mean ± SD)	8.0 ± 8.1	8.3 ± 8.7	7.8 ± 7.7	0.72
Psychological symptoms				
Depression[d]	28 (18.3%)	21 (31.3%)	7 (8.2%)	<0.01
COVID-induced PTSD[e]	36 (23.5%)	26 (39.4%)	10 (11.8%)	<0.01

Abbreviations: PTSD, Posttraumatic Stress Disorder; PHQ-8, Patient Health Questionnaire (8-item); PCL-5, PTSD Checklist for DSM-5.
[a] Missing responses for 8 (5.2%) patients.
[b] Patients could select more than one response.
[c] Missing responses for 9 (5.9%) patients.
[d] PHQ-8 score ≥ 10.
[e] PCL-5 score ≥ 30.
[f] Fisher's exact test.

4. Discussion

Nearly half of patients discharged home after COVID-19 illness reported cognitive deficits three months later. Psychological factors (i.e., current depression, COVID-induced PTSD, prior mental illness) were robustly associated with cognitive symptoms. Cognitive symptoms were highly prevalent, even among patients who did not require critical care. Our results are consistent with other studies describing cognitive deficits in young, otherwise healthy patients with brief COVID-19 hospitalizations [4,6–9]. We extend these findings by demonstrating that such cognitive symptoms are closely correlated with psychological distress.

The odds of persistent cognitive symptoms were five-fold greater in patients with concurrent depression and nearly four-fold greater in patients with COVID-induced PTSD. Since cognitive impairment is a common feature of both depression and PTSD [14], it is possible that these cognitive symptoms were manifestations of underlying depression and/or PTSD, further exacerbated by the experience of COVID-19 and its sequelae. Alternatively, cognitive symptoms may have been a primary consequence of COVID-19, via direct neuropathogenic effects [15–19] or indirect systemic derangements (e.g., hypoxia, inflammation, coagulopathy, cytokine storm) [19–22]. Neuropsychiatric and neurocognitive symptoms of COVID-19 are thought to develop via similar mechanisms [23–25], which may at least partially explain the robust associations observed here. Additionally, the experience of COVID-19 hospitalization – often involving invasive procedures, prolonged sedation, social isolation, and real or perceived threat of mortality – may

Table 2
Demographic and clinical correlates of cognitive symptoms three months after COVID-19 illness (n = 153).

Characteristic	Unadjusted OR	95% CI	*P*-value	Adjusted OR	95% CI	P value
Age (per 1-year increase)	1.02	1.00–1.05	0.07	1.03	0.99–1.06	0.11
Female (vs. male)	2.12	1.08–4.16	0.03	1.71	0.61–4.78	0.31
Black (vs. non-Black)	1.44	0.59–3.51	0.42	1.35	0.35–5.16	0.67
Hispanic (vs. non-Hispanic)	0.78	0.41–1.48	0.45	0.61	0.20–1.83	0.38
Employed (vs. unemployed)	0.92	0.48–1.76	0.79	1.24	0.42–3.69	0.70
Length of hospitalization[a]	1.01	0.96–1.06	0.71	1.01	0.95–1.08	0.68
Prior mental illness	4.62	1.70–12.56	<0.01	4.90	1.24–19.41	0.02
Depression[b]	5.09	2.01–12.89	<0.01	5.15	1.30–20.35	0.02
COVID-induced PTSD[c]	4.88	2.14–11.11	<0.01	3.67	1.13–11.89	0.03

Abbreviations: PTSD, Posttraumatic Stress Disorder; PHQ-8, Patient Health Questionnaire (8-item); PCL-5, PTSD Checklist for DSM-5.
[a] Days hospitalized for COVID-19 illness.
[b] PHQ-8 score ≥ 10 vs. PHQ-8 score < 10.
[c] PCL-5 score ≥ 30 vs. PCL-5 score < 30.

contribute to immediate or delayed neuropsychiatric repercussions via sympathetic system activation, stress hormone release, formation of traumatic memories, or other unrecognized factors [19,23–25]. A deeper understanding of the mechanistic relationship between the psychological and cognitive sequelae of COVID-19 will require detailed neuropsychological assessments to confirm self-reported symptoms, as well as neuroimaging for clinical correlation, neither of which is routinely performed post-COVID [3].

Study strengths included the diverse population and use of validated psychological instruments for assessing current depression and COVID-induced PTSD. Limitations included the cross-sectional design, small sample, and modest participation rate. Therefore, prevalence estimates should be interpreted with caution and may not be generalizable to all post-COVID patients. Cognitive symptoms were not determined using formal neuropsychological assessment and thus may not represent true cognitive impairment. Data on pre-existing cognitive disorders and delirium during the COVID-19 illness were unavailable and may have confounded the observed associations. Because few patients required ICU admission or intubation, results may not be generalizable to the most severe forms of COVID-19. Larger prospective studies with repeated assessments and longer follow-up are needed to better characterize the predictors, duration, and consequences of COVID-related cognitive symptoms.

Our findings add to the growing body of knowledge surrounding long-term neurocognitive and neuropsychiatric effects of COVID-19. While our prevalence estimates should be interpreted cautiously given our convenience sample, the high frequency of cognitive and psychological symptoms observed months after non-critical COVID-19 illness highlights the importance of comprehensive neurocognitive testing and depression/PTSD screening as part of standard post-COVID care. Furthermore, the strong association of depression and COVID-induced PTSD with cognitive symptoms suggests that enhanced detection and treatment of such psychological symptoms could improve cognitive outcomes in patients recovering from COVID-19.

Author contributions

Dr. Liyanage-Don designed and conceptualized the study, analyzed and interpreted the data, drafted the manuscript, and revised the manuscript for intellectual content. Dr. Winawer, Dr. Hamberger, and Dr. Agarwal revised the manuscript for intellectual content. Ms. Trainor and Ms. Quispe played a major role in the acquisition of the data. Dr. Kronish designed and conceptualized the study, helped to interpret the data, and revised the manuscript for intellectual content.

Data statement

Data are available from the authors upon request.

Declaration of Competing Interest

The authors have no competing interests to report.

Data availability

Data will be made available on request.

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