


SHORT COMMUNICATION

Anxiety and depression symptoms after virological clearance of COVID-19: A cross-sectional study in Milan, Italy

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Abstract

Prevalence of anxiety or depression was investigated in 105 coronavirus disease 2019 (COVID-19) patients at 1 to 3 months from virological clearance by hospital anxiety and depression scale (HADS-A/D). 30% of patients displayed pathological HADS-A/D, 52.4% showed persistent symptoms. Pathological patients with HADS-A/D more commonly reported symptom persistence, even after adjustment for age, gender, and disease severity. Psychological assessments should be encouraged in COVID-19 patients' follow-up.

KEYWORDS

anxiety and depression symptoms, COVID-19, hospital anxiety and depression scale

1 | INTRODUCTION

An outbreak of novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has emerged in Northern Italy at the beginning of 2020, following an earlier epidemic in China. The infection may result in a severe systemic disease affecting a number of organs, first of all lungs. Thus, it is crucial to arrange a follow-up of recovered patients to early identify possible organ damage and long-term sequelae.¹

To date, data on follow-up of patients recovered from coronavirus disease 2019 (COVID-19) are missing; the first case series described that symptoms, such as fever, cough, and fatigue, could persist after hospital discharge.² In addition to multiorgan impairment, possible psychological consequences need to be addressed.¹ Recently, a nationwide survey among Italian population showed that a high proportion of people suffered from anxiety and depression during the epidemics,³ even if not affected by COVID-19 disease. Preliminary data suggest that anxiety and depression might also persist in patients recovering from COVID-19.⁴ Psychological distress is therefore an important concern for patients with COVID-19 and should not be neglected during hospitalization and follow-up. In this context, we aimed to investigate prevalence and possible predictors of anxiety and depression after clinical and virological recovery from COVID-19 disease.

2 | METHODS

Cross-sectional study including patients with documented clinical recovery and virological clearance after hospitalization for COVID-19 disease at S. Paolo and S. Carlo Hospitals in Milan from April to June 2020. Clinical recovery was defined as absence of fever for 48 to 72 hours and normal oxygen saturation on ambient air with concomitant hospital discharge. Virological clearance was defined as presence of two consecutive negative nasopharyngeal swabs taken 24 to 48 hours apart, at least 14 days after clinical recovery.

One to 3 months after virological clearance patients underwent a medical examination including: persistence or resolution of physical symptoms (fever, gastro-intestinal symptoms, at rest and exertional dyspnea, asthenia, anosmia/dysgeusia, pain, cognitive deficits defined as memory disorders, vital signs and peripheral oxygen saturation). Patients also completed the hospital anxiety and depression scale (HADS) questionnaire to investigate psychological symptoms (anxiety and depression): a score ≥ 8 for anxiety and depression was considered as borderline/pathological. Lastly, the presence of cognitive disorders in patients over 65 years was evaluated by mini mental state examination (MMSE) (a corrected score of ≤ 25 was considered pathological).⁵

Symptom persistence was defined as the reported persistence of at least one physical symptom among those investigated. All data were recorded on an electronic case report form. Mann-Whitney test, the χ^2 test or Fisher's Exact test were used for statistics, as appropriate; correction for confounders was made by multivariable logistic regression analysis.

3 | RESULTS

A total of 105 patients were enrolled; patients' characteristics are shown in Table 1: 73% were male, median age was 55 years (interquartile range [IQR]: 43-65). All patients displayed interstitial pneumonia at hospital admission. As regards disease severity during the acute phase, 72.4% of subjects needed low-flow oxygen or no oxygen therapy, while 27.6% required continuous positive airway pressure systems, noninvasive mechanical ventilation or orotracheal intubation (Table 1).

Only 6 out of 105 (5.7%) and 3 out of 105 (2.8%) patients were being treated with antidepressant and anxiolytic therapies before admission, respectively. Patients underwent medical examination a median of 46 (IQR: 43-48) days after virological clearance.

A total of 100 out of 105 (95.2%) patients completed HADS questionnaire (five foreigners subjects were not able to complete it for language reasons); anxiety items in HADS (HADS-A) were abnormal in 29 out of 100 (29%) patients, while depression items (HADS-D) in 11 out of 100 (11%). HADS-A/D (at least one of the two scales) resulted pathological in one-third (30/100, 30%) of patients, of which 10 out of 30 (33%) presented both anxiety and depression, 19 out of 30 (63%) had only anxiety and 1 out of 30 (4%) only depression. Patients with pathological HADS-A/D did not differ in demographic and clinical parameters or in disease severity, compared to subjects with a normal HADS-A/D score (Table 1).

Interestingly, more than half of the patients (55/105, 52.4%) reported persistence of physical symptoms at the follow-up visit: patients with abnormal HADS-A/D showed a higher proportion (77% vs 43%; $P = 0.002$) of physical symptoms persistence, compared to subjects displaying normal HADS-A/D (Table 1). Looking at individual symptoms, 31.4% of patients reported ongoing asthenia and 27.6% dyspnea; these symptoms were more commonly reported by patients with pathological HADS-A/D (Table 1).

Finally, 17.1% of patients complained persistent cognitive disorders, once again more frequently in those with altered HADS-A/D (36.7% vs 10%). Among 25 patients who performed MMSE, 10 (40%) patients had scores that were compatible with mild or worst cognitive impairment, without differences between the two groups (Table 1).

In the multivariable logistic regression analysis, the persistence of physical symptoms was confirmed to be independently associated with anxiety and depression (ie, abnormal HADS-A/D) (AOR, 4.51; 85% confidence interval: 1.56-13.05; $P = .006$), after adjusting for age, gender, and severity of disease.

4 | DISCUSSION

HADS is a validated tool designed to detect anxiety and depression symptoms in hospitalized patients.⁶ To date, few studies investigated psychological consequences of COVID-19 pandemics by HADS-A/D.^{7,8} In most cases mental health status of general population or of health care workers was assessed via online surveys, highlighting substantial rates of disorders, especially anxiety.⁷ Kong et al described that, among 144 hospitalized patients diagnosed with SARS-CoV-2 infection, 34.7% and 28.5% of subjects obtained pathological HADS scores for anxiety and depression, respectively.⁹ These data are compatible with those observed in our cohort of patients recovered from COVID-19. As reported in a recent metanalysis by Rogers et al, psychological and neuropsychiatric alterations were commonly detected during both acute and post-acute disease stages (between 60 days and 12 years after the infection) in SARS and Middle East respiratory syndrome epidemics and similarly in acute phase of SARS-CoV-2 disease. The authors concluded that follow-up data concerning patients with SARS-CoV-2 are still lacking.⁴ Thus, our preliminary data will try to fill this gap.

By administering HADS-A/D to subjects clinically and virologically recovered from SARS-CoV-2 pneumonia, we detected a substantial proportion of patients still suffering from anxiety (29%) and depression (11%) symptoms. Moreover, subjects with pathological HADS-A/D scores complained persistence of any physical symptoms more frequently than patients with normal scores. In particular, ongoing asthenia, dyspnea, and cognitive deficits were the predominant symptoms. Contrary to our expectations, we did not find any correlation between the severity of disease in the acute phase, and anxiety/depression, possibly due to the limited number of severe cases included in this analysis.

We found 17% of subjects reporting cognitive disorders; direct viral invasion of central nervous system or immune responses triggered by the infection may lead to brain damage with subsequent cognitive impairment and psychological distress.¹⁰

This study has some limitations: (a) only patients with confirmed virological recovery (negative SARS-CoV-2 PCR on respiratory specimens on two consecutive samples after clinical resolution) were included in the study, while it could be interesting to study anxiety/depression symptoms also in subjects with persistent positive PCR after clinical recovery; (b) sample size is limited, our results need to be confirmed when the follow-up of a larger population will be available; (c) baseline (pre-COVID-19) psychological evaluation of the study population was not available, so that no causality hypothesis among anxiety or depression and persistence of physical symptoms can be speculated; (d) data concerning SARS-CoV-2 infection and outcome in other family members, as well as level of education, a factor known to be positively correlated to anxiety levels, were not available.

In conclusion, a considerable proportion of patients with COVID-19 still experienced psychological distress and ongoing physical symptoms after hospital discharge, underlining the complexity of patients with COVID-19 management even after clinical and virological

TABLE 1 Demographic and clinical characteristics of the study population

Demographic parameters	Study population (N = 105)	Normal HADS-A/D ^a (N = 70)	Pathological HADS-A/D ^a (N = 30)	P values
Age, y	55 (43-65)	55 (42-64)	55 (45.5-66)	.976
Gender				.111
Male	77 (73.3%)	55 (78.6%)	19 (63.3%)	.111
Charlson comorbidity score	1 (0-2.5)	1 (0-3)	1 (0-2)	.798
In-hospital parameters				
Oxygen therapy:				.806
None, low-flow oxygen therapy	76 (72.4%)	52 (76.5%)	20 (74.1%)	
CPAP, NIV, OTI	24 (22.9%)	16 (23.5%)	7 (25.9%)	
Length of hospital days (LOS)	8 (6-11)	8 (6-12)	8 (5.75-10)	.831
Follow-up visit				
Time since virological clearance, days	46 (43-48)	46 (43-48)	46 (44-49)	.317
Symptoms at follow-up visit:				
Symptoms' persistence ^b	55 (52.4%)	30 (42.9%)	23 (76.7%)	.002
Anosmia:				.826
No, ever	44 (41.9%)	30 (42.9%)	13 (43.3%)	
Ongoing	6 (5.7%)	4 (5.7%)	2 (6.7%)	
Resolved	51 (48.6%)	34 (48.6%)	15 (50%)	
Unknown	4 (3.8%)	2 (2.9%)	0	
Dysgeusia:				.697
No, ever	39 (37.1%)	25 (35.7%)	13 (43.3%)	
Ongoing	6 (5.7%)	4 (5.7%)	1 (3.3%)	
Resolved	57 (54.3%)	39 (55.7%)	16 (53.3%)	
Unknown	3 (2.9%)	2 (2.9%)	0	
Gastro-intestinal symptoms:				.02
No, ever	62 (59%)	49 (70%)	13 (43.3%)	
Ongoing	1 (1%)	0	1 (3.3%)	
Resolved	37 (35.2%)	21 (30%)	16 (53.3%)	
Unknown	5 (4.8%)	0	0	
Fever:				.26
No, ever	8 (7.6%)	7 (10%)	1 (3.3%)	
Ongoing	0	0	0	
Resolved	92 (87.6%)	63 (90%)	29 (96.7%)	
Unknown	5 (4.8%)	0	0	
Burning pain:				.091
No, ever	69 (65.7%)	52 (74.3%)	17 (56.7%)	
Ongoing	11 (10.5%)	5 (7.1%)	6 (20%)	
Resolved	19 (18.1%)	13 (18.6%)	6 (20%)	
Unknown	6 (5.7%)	0	1 (3.3%)	
Dyspnea:				.034
No, ever	30 (28.6%)	19 (27.1%)	6 (20%)	
Ongoing	7 (6.7%)	13 (18.6%)	14 (46.7%)	
Resolved	62 (59%)	37 (52.9%)	10 (33.3%)	
Unknown	6 (5.7%)	1 (1.4%)	0	
Asthenia:				.044
No, ever	29 (27.6%)	24 (34.3%)	5 (16.7%)	
Ongoing	33 (31.4%)	18 (25.7%)	15 (50%)	
Resolved	38 (36.2%)	28 (40%)	10 (33.3%)	
Unknown	5 (4.8%)	0	0	

(Continues)

TABLE 1 (Continued)

Demographic parameters	Study population (N = 105)	Normal HADS-A/D ^a (N = 70)	Pathological HADS-A/D ^a (N = 30)	P values
Cognitive deficits (memory disorder):				.002
No, ever	75 (71.4%)	60 (87.5%)	15 (50%)	
Ongoing	18 (17.1%)	7 (10%)	11 (36.7%)	
Resolved	4 (3.8%)	2 (2.9%)	2 (6.7%)	
Unknown	8 (7.6%)	1 (1.4%)	2 (6.7%)	
Other ^c :				.122
No, ever	34 (32.4%)	56 (80%)	19 (63.3%)	
Ongoing	18 (17.1%)	9 (12.9%)	9 (30%)	
Resolved	7 (6.7%)	5 (7.1%)	2 (6.7%)	
MMSE ^d (N = 25):				.818
Normal (26-30)	11/25 (44%)	7/16 (43.8%)	4/9 (44.4%)	
Mild cognitive deficits (18-25)	9/25 (36%)	6/16 (37.5%)	3/9 (33.3%)	
Pathological (<18)	1/25 (4%)	1/16 (6.3%)	0	
Unknown	4/25 (16%)	2/16 (12.5%)	2/9 (22.2%)	

Note: Quantitative variables are presented as median, (interquartile range); categorical variables are presented as absolute numbers, (percentages).

Bold values are P values <.05 and ongoing symptoms at the follow up visit.

Abbreviations: CPAP, continuous positive airway pressure; HADS, hospital anxiety and depression scale; MMSE, mini mental state examination; NIV, noninvasive ventilation; NSTEMI, non-ST elevation myocardial infarction; OTI, orotracheal intubation.

^aHADS-A/D, a score ≥ 8 in the scale for anxiety (A) and in the scale for depression (D) was considered altered (borderline/pathological).

^b'Symptoms' persistence: persistence of at least one symptom among those investigated including fever, gastro-intestinal symptoms, at rest and exertional dyspnea, asthenia, anosmia/dysgeusia, pain, cognitive deficits defined as memory disorders, other.

^cOther symptoms included: chest pain, headache, constipation, tinnitus, insomnia, palpitations, NSTEMI, cough, sore throat.

^dMMSE (adjusted for age and education years).

recovery, and the need of long-term follow-up within multidisciplinary teams.¹¹

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

AM and FB developed the concept of this study. DT, RC, DB, DM, CF, and GM collected data on case report form. AT performed data entry and FB did the statistical analyses. DT, FB, RC, and DB wrote the short report. DT, FB, RC, DB, GM, EV, and AM contributed to the final text. All the authors have read and approved the final text.

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