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CORRESPONDENCE

Systemic consequences of COVID-19 infection in patients requiring mechanical ventilation: a 12-month prospective study

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Dear Editor,

Previous reports described the long-term systemic consequences of COVID-19 infection [1–4]. Several conditions have been evaluated as part of post-COVID syndrome. In most of cohorts studied, symptoms persisted for a long time in a large number of subjects; in particular, a recent study from Wuhan assessed that about half of subjects included had COVID-related symptoms at 3 months and 28.2% at 12 months [1]. However, in this cohort, only a minority of patients had a critically ill disease requiring mechanical ventilation at the time of hospitalization and no specific data were described for this group of patients. Recently, we read with attention the comprehensive review by Akbarialiabad et al. [5] that included a large number of studies; authors stated that several controversies are present in most of studies, leading to a difficult diagnosis and to a consequent difficult management of these subjects. In particular, no definitive study addressed to date the clinical consequences of COVID-19-related symptoms in patients with very severe disease at presentation. In this paper, we evaluated the long-term persistence of clinical, radiological and functional consequences of COVID-19-related symptoms in patients requiring mechanical ventilation at the time of hospitalization.

We describe here a cohort of 59 consecutive patients hospitalized for SARS CoV-2 pneumonia requiring mechanical ventilation from March to December 2020. At the time of discharge, patients were asked to be followed up in a post-COVID outpatient clinic for the next 12 months at Garbagnate Milanese Hospital, Milan, Lombardy. During hospitalization, all patients underwent a chest computed tomography (CT) scan and most of them were treated with intravenous dexamethasone. The duration of steroid and other COVID-19 treatments (i.e., hydroxychloroquine, lopinavir/ritonavir and azithromycin in the period of March–April 2020; remdesivir at October–December 2020) was not standardized at the time of hospitalization. Patients with a documented SARS CoV-2 re-infection were not included in the study. Follow-up visits were planned at 3, 6 and 12 months after discharge; at same time-points, patients repeated a chest computed tomography (CT) scan and were tested for pulmonary function through spirometry, 6-min walking test (6MWT) and DLCO (diffusing capacity of the lung for carbon monoxide). We recorded all clinical symptoms reported by the patients during the planned visits. The outcomes of COVID-19-related symptoms and chest CT abnormalities were compared between different groups. McNemar test was used to compare variables at the different time-points.

Mean age was 59 years (95% CI 39–75) and 42 subjects (79.2%) were males. Main co-morbidities were hypertension ($n = 31$) and diabetes ($n = 11$); 7 patients (13.2%) had underlying pulmonary diseases as asthma ($n = 4$), chronic obstructive pulmonary disease (COPD, $n = 2$) or emphysema ($n = 1$). Mean hospital stay during COVID-19 infection was 32 days (95% CI 19–94); main complications during hospitalization were infections (as fungal or bacterial infections, $n = 13$, 24.5%), cardiovascular (as pulmonary embolism, angina or atrial fibrillation, $n = 11$, 20.7%) and renal failure ($n = 6$, 11.3%).

Table 1 summarized the evolution of symptoms throughout the entire study period. At 3 months, main reported symptoms were hair loss ($n = 34$, 64,1%), dyspnea ($n = 23$, 43.4%), fatigue ($n = 20$, 37.7%) and heart palpitation ($n = 19$, 35.8%). At 12 months, dyspnea ($n = 16$, 30.2%) and heart palpitation ($n = 13$, 24.5%) persisted in a discrete number of individuals and 14 subjects (26.4%) did not report any symptoms. Some symptoms, though

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Table 1 Evolution of clinical symptoms in 53 COVID-19-infected patients requiring mechanical ventilation

Clinical symptoms (*n*, %)	Month 3 (*n* = 53)	Month 6 (*n* = 53)	Month 12 (*n* = 53)	*p*
Hair loss	34 (64.1)	8 (15.1)	0 (0)	< 0.001
Dyspnea	23 (43.4)	21 (39.6)	16 (30.2)	ns
Fatigue	20 (37.7)	7 (13.2)	5 (9.4)	ns
Heart palpitation	19 (35.8)	18 (34.0)	13 (24.5)	ns
Headache	8 (15.1)	3 (5.7)	2 (3.8)	ns
Myalgia	8 (15.1)	5 (9.4)	2 (3.8)	ns
Chest pain	5 (9.4)	3 (5.7)	3 (5.7)	ns
Insomnia	4 (7.5)	2 (3.8)	2 (3.8)	ns
Memory loss	4 (7.5)	4 (7.5)	4 (7.5)	ns
Anosmya/dysgeusia	3 (5.7)	1 (1.9)	1 (1.9)	ns
Others	7 (13.2)	4 (7.5)	2 (3.8)	ns

Clinical symptoms "others" include: nausea/vomiting, dizziness, diarrhea, pruritus, joint pain

unusual as memory loss, when reported at month 3 usually persisted at month 12, whilst others as hair loss resolved in all patients.

At hospitalization, almost all patients had ground glass opacities at chest CT scan and 38 of them (71.7%) had ≥ 3 abnormalities (Table 2). Radiologic patterns modified during follow-up; at month 3, fibrous stripes were described in 39 (73.6%), ground glass opacity in 34 (64.1%), nodules in 28 (52.8%) and patchy shadows in 21 subjects (39.6%). No patient had a complete recovery of chest abnormalities at month 3, and ≥ 3 abnormalities were observed in 24 (45.3%). At month 12, lung CT scan was still abnormal in most of patients (*n* = 48, 90.6%), with persistence of fibrous stripes (*n* = 30, 56.6%) and nodules (*n* = 22, 41.5%) as main alterations; ≥ 3 abnormalities were found in 14 patients (26.4%).

At month 3, spirometry was normal in all but one subject with underlying COPD who had a mild obstructive pattern; DLCO was moderately to severely reduced in 29 (54.7%) and 6MWT in 7 subjects (13.2%). At month 12, DLCO was still reduced in 4 subjects (7.5%); spirometry and 6MWT completely recovered in all patients without specific treatment.

Taken together, these data demonstrated that in patients with severe SARS CoV-2 pneumonia needing mechanical ventilation different symptoms may persist up to 12 months; some of these symptoms like hair loss are fully reversible in all patients, whilst others, like memory loss, are not. Further, lung abnormalities persisted at chest CT scan after 12 months in the majority of patients and some of these, as bronchiectasis or pleural thickening and adhesions, seem irreversible; the future evolution and the clinical significance of these findings remain unknown. Nevertheless, a very limited number of subjects had an impairment of pulmonary function at 12 months, suggesting a discrepancy between the persistence of clinical symptoms, the radiological findings and the results of functional tests.

Our study has some limitations. First, we did not use a validated questionnaire to assess clinical symptoms, but we recorded only those reported by the patients during the medical visits. Second, this mono-center study included only patients needing mechanical ventilation at the beginning of the pandemic. Third, our study included only patients hospitalized in 2020, prior of the implementation of COVID-19 vaccination. Consequently, our results could be not

Table 2 Evolution of radiological findings in 53 COVID-19-infected patients requiring mechanical ventilation

Radiological findings (*n*, %)	Baseline (*n* = 53)	Month 3 (*n* = 53)	Month 6 (*n* = 53)	Month 12 (*n* = 53)	*p*
Fibrous stripes	19 (35.8)	39 (73.6)	31 (58.5)	30 (56.6)	ns
Ground glass opacity	52 (98.1)	34 (64.1)	16 (30.2)	7 (13.2)	< 0.001
Nodules	7 (13.2)	28 (52.8)	26 (49.1)	22 (41.5)	0.04
Patchy shadows	22 (41.5)	21 (39.6)	12 (22.6)	10 (18.9)	ns
Pleural thickening and adhesions	2 (3.8)	13 (24.5)	11 (20.7)	11 (20.7)	ns
Bronchiectasis	1 (1.9)	10 (18.9)	10 (18.9)	10 (18.9)	ns
Others	20 (37.7)	8 (15.1)	4 (7.5)	3 (5.7)	0.02
> 3 Abnormalities	38 (71.7)	24 (45.3)	19 (35.8)	14 (26.4)	0.01
Normal	0 (0)	0 (0)	2 (3.8)	5 (9.4)	ns

Radiological findings "others" include: pleural or pericardiac effusion, calcification, pulmonary bullae, emphysema

applicable in the future, due to the less severity of SARS CoV-2 infection associated with the new variants of the virus in the context of large-scale vaccination.

Despite these clear limitations, some conclusions can be drawn. Our study included patients that were systematically followed by clinical, functional and radiological point of view for a long period of time (12 months); therefore, our findings are highly representative of the subjects who developed SARS CoV-2 pneumonia at the beginning of the pandemic. These data confirm that after the acute phase of SARS CoV-2 pneumonia that is usually associated with the respiratory impairment, several different clinical symptoms can develop and persist for a long period. Nevertheless, an impairment of pulmonary function seems unusual 1 year after SARS CoV-2 pneumonia, despite the persistence of radiological abnormalities. A longer follow-up is needed to better understand if clinical symptoms and radiological abnormalities that are still present at month 12 will become chronic or will slowly recover. Consequently, the management of these abnormalities could be an important healthcare challenge in the future.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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