COVID-19 severity impacts on long-term neurological manifestation after hospitalisation

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ABSTRACT

**Background:** Preclinical and clinical investigations have argued for nervous system involvement in SARS-CoV-2 infection and for long term sequelae including neurological manifestations.

**Methods:** A sample of 208 previously hospitalized COVID-19 patients, 165 patients were reassessed at 6 months according to a structured standardized clinical protocol. Premorbid comorbidities and clinical status, severity of COVID-19 disease, complications during and after hospitalization were recorded.

**Results** At 6-month follow-up after hospitalisation due to COVID-19 disease, patients displayed a wide array of neurological symptoms, being fatigue (34%), memory/attention (31%), and sleep disorders (30%) the most frequent. Subjects reporting neurological symptoms were affected by more severe respiratory SARS-CoV-2 infection parameters during hospitalisation. At neurological examination, 37.4% of patients exhibited neurological abnormalities, being cognitive deficits (17.5%), hyposmia (15.7%) and postural tremor (13.8%) the most common. Patients with cognitive deficits at follow-up were comparable for age, sex and pre-admission comorbidities but experienced worse respiratory SARS-CoV-2 infection disease and longer hospitalisation.

**Conclusions:** Long term neurological manifestations after hospitalization due to COVID-19 infection affects one third of survivors. Multiple neurological abnormalities including mild cognitive impairment are associated with severity of respiratory SARS-CoV-2 infection.
INTRODUCTION

After the first cases of the novel coronavirus disease 2019 (COVID-19) were reported in Wuhan, China, in December 2019, the spread rapidly became a pandemic, involving millions of cases worldwide. With the increasing number of confirmed cases and the accumulating clinical data, it is now well established that, in addition to the predominant respiratory symptoms, a significant proportion of COVID-19 patients experience neurological symptoms and syndromes. Clinical findings on previously hospitalised and non-hospitalised patients with COVID-19 reported the persistence of multiple symptoms, particularly fatigue and dyspnoea. Accordingly, some authors have suggested the so-called, but not yet defined, “post-COVID-19 syndrome” based on symptoms reported after three months of SARS-CoV-2 infection. Few follow-up studies, however, have investigated patients discharged from hospital after recovery from COVID-19 and no data about persistent neurological manifestations are available yet.

In this study, subjects previously hospitalised for COVID-19 disease entered a longitudinal study in order to evaluate neurological manifestations after 6 months of follow-up and their potential relationship with pre-morbid conditions and severity of SARS-CoV-2 infection.

METHODS

All COVID-19 survived patients without pre-morbid neurological disease discharged between February and April 2020 from a COVID-19 Unit of the ASST Spedali Civili Hospital were asked to participate to a follow-up study including a standardised medical and neurological symptoms checklist and a neurological examination at 6 months. Premorbid conditions were recorded at admission using the Cumulative Illness rating scale (CIRS). Hospitalisation data included the
severity of COVID-19 disease, classified according to the Brescia-COVID Respiratory Severity Scale (BCRSS\(^7\)), assigning one point to i) dyspnoea ii) respiratory rate > 22 iii) PaO2<65 mmHg or SpO2 <90% iv) worsening of interstitial pneumonia at X-ray and the risk of deterioration with the quick Sequential Organ Failure Assessment (qSOFA) score\(^8\).

At follow-up, data were collected using a neurological checklist including symptoms related to central, peripheral, myopathic and cognitive manifestations, whereas the neurological examination assessed cranial nerves, motor, sensory, cerebellar, basal ganglia-related function, deep tendon reflexes, pyramidal signs and global cognitive function using the Montreal Cognitive Assessment (MoCA). The study was approved by the local ethics committee of ASST “Spedali Civili di Brescia” Hospital and the requirement for informed consent was waived by the Ethics Commission (NP 4166).

**Statistical analysis**

Differences between patients according to COVID-19 respiratory severity (BCRSS) and the association with neurological complaints were evaluated by Fisher’s exact test or ANOVA with Bonferroni correction for dichotomic and continuous variables, respectively. Logistic regression analyses were performed in order to evaluate demographics and clinical predictors (including age, sex, CIRS, days of hospitalisation, O2 treatment and BCRSS) of the presence of i) neurological complaints or ii) neurological features at examination (separately for the most common symptoms and features reported).

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**RESULTS**

From a sample of 208 consecutively hospitalized patients for COVID-19 disease, 33 deceased during hospitalisation. Survivors were younger (p=0.001; 65.7±12.6 vs 78.6±8.6) and exhibited less
comorbidities (p=0.004, mean CIRS 1.36±0.51 vs 1.51±0.4) in front of similar COVID-19 severity compared to deceased patients. Out of 175 survivors, five patients died after discharge, three had a previous diagnosis of dementia and two refused to participate, resulting in a final sample of 165 patients included (supplementary Figure 1). Patients stratified according to COVID-19 severity (BCRSS) differ for number of days of hospitalisation, O2 treatment and qSOFA but not for age or premorbid total and severity comorbidity index (Table 1).

At follow-up, the most common symptoms reported were fatigue (34%), memory complaints (31%), sleep disorders (30.8%) and myalgias (29.6%), followed by depression/anxiety, visual disturbances, paraesthesia and hyposmia (Figure 1, supplementary Table 1). Patients with higher BCRSS reported higher number of symptoms at follow-up (p=0.004), memory complaints (p=0.015) and visual disturbances (p=0.006) after correction for age and CIRS. By logistic regression analyses age (p=0.028) and O2 treatment (p=0.04) were identified as best predictors of memory complaints.

One-hundred-five patients were further evaluated in presence by a standard neurological examination and cognitive screening; no difference was found between the two sub-groups of patients (visited vs refusals) in term of age, sex distribution, pre-morbid CIRS, severity of COVID-19 and reported neurological symptoms. At standard examination, 42 exhibited neurological abnormalities, namely dysgeusia/hyposmia (n=19), enhanced physiological tremor (n=15), low-limb hypoesthesia (n=6), low-limb motor deficits (n=3) and cognitive deficits (n=17) according to MoCA Italian validated norms. Neurological abnormalities at examination were associated with older age (p=0.005), higher pre-morbid comorbidity index (p=0.001), worse BCRSS (p=0.05), longer hospitalisation duration (p=0.002) and higher number of neurological symptoms reported (p=0.007) (supplementary Table 2). Logistic regression identified duration of hospitalisation (p=0.02) and pre-morbid comorbidity index (p=0.03) as predictors of neurological abnormalities. Severity of COVID-19 disease and duration of hospitalisation (p=0.002 for both) were the best
predictors of abnormal MoCA after adjusting for age, sex and premorbid comorbidities in logistic regression analyses.

**DISCUSSION**

Findings showed that previously hospitalized COVID-19 patients reported a wide array of neurological symptoms six months after SARS-CoV-2 infection, predicted by combination of age, premorbid conditions and severity of disease.

These findings extend recent studies which have argued for a high prevalence of Post-COVID clinical manifestation and claimed that long term consequences of COVID-19 involve both central and peripheral nervous systems\(^1,2,10,11\). In particular, Goertz and coauthors\(^5\) reported common persistent symptoms about 3 months after COVID-19 onset in a large survey of previously hospitalised and non-hospitalised patients. Similarly, Carfi and co-authors\(^4\) found that in patients hospitalized for COVID-19 disease, 87% reported persistence of at least one symptom, particularly fatigue and dyspnoea - about 60 days after discharge.

In the present cohort of patients with six months of follow-up, the most prevalent symptoms reported were fatigue, memory complaints, sleep disorders and myalgias followed by depression/anxiety, visual disturbances, paraesthesias and hyposmia. Long-term neurological complaints showed different distributions according to COVID-19 severity, whereas age and oxygen treatment were the best predictors in logistic regression analyses. The neurological examination revealed hyposmia, cognitive impairment and postural tremor as the most prevalent features. Longer hospitalization and premorbid conditions were the strongest predictors of neurological abnormalities at examination, whereas cognitive impairment was specifically associated with severity of COVID-19 independently from age and pre-morbid conditions. On one
hand, this suggest that hospitalization and severity of COVID-19 have a large impact in subjects with increased multimorbidity, in line with other infectious diseases, such as community-acquired pneumonia. On the other, the persistence of observed cognitive deficits needs to be addressed in COVID-19 follow-up programs in order to specifically evaluate their impact and progression over-time and disentangle their potential relationship with psychosocial and psychiatric disturbances. Several limitations should also be acknowledged. First, pre-morbid conditions were based on medical records and assessment during hospitalisation thus not allowing an extensive neurological and psychiatric screening at the baseline. Second, in this study patients with neurological diseases developed during the acute phase of SARS-CoV-2 infection were not considered, thus potentially underestimate the global neurological burden due to COVID-19. Furthermore, this is a single-center study with a relatively small sample size and large studies including non-hospitalized patients are warranted to confirm the present data.

Limitations notwithstanding, our findings indicate that several neurological features are a relevant component of long-term manifestations of COVID-19 disease even in less severe patients, thus suggesting the importance of long-term follow-up programs to properly care patients and to be able to evaluate the real impact of SARS-CoV-2 infection on brain health status that is still uncertain.

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FIGURE LEGEND

**Figure 1** Prevalence of neurological symptoms in the whole samples and in subgroups of patients stratified by COVID-19 severity. **Abbreviations:** BCRSS, Brescia-COVID Respiratory Severity Scale; IADL, instrumental activities of daily living
| Symptoms reported at 6 months | Symptoms reported according to COVID-19 severity |
|------------------------------|-----------------------------------------------|
| **Total (n=165)**           | **BCRSS 3 (n=31)**                            |
| Fatigue                      | Fatigue                                      |
| 34,1%                        | 48,4%                                        |
| Memory complaints             | Memory complaints                             |
| 30,8%                        | 48,4%                                        |
| Sleep disorders              | Sleep disorders                              |
| 30,8%                        | 38,7%                                        |
| Myalgia                      | Myalgia                                      |
| 29,6%                        | 32,3%                                        |
| Depressive symptoms/anxiety  | Depressive symptoms/anxiety                   |
| 26,0%                        | 32,3%                                        |
| Loss of dependency in IADL   | Loss of dependency in IADL                    |
| 20,7%                        | 32,4%                                        |
| Blurring/loss of vision       | Blurring/loss of vision                       |
| 19,5%                        | 38,7%                                        |
| Numbness/tingling             | Numbness/tingling                             |
| 18,3%                        | 22,6%                                        |
| Hyposmia/hypogeusia           | Hyposmia/hypogeusia                           |
| 16,5%                        | 25,8%                                        |
| Urinary dysfunction           | Urinary dysfunction                           |
| 14,0%                        | 16,1%                                        |
| Confusion/Dizziness           | Confusion/Dizziness                           |
| 13,0%                        | 25,8%                                        |
| Dizziness/Hypotension         | Dizziness/Hypotension                         |
| 12,2%                        | 19,4%                                        |
| Gait disturbances             | Gait disturbances                             |
| 10,7%                        | 12,9%                                        |
| Abnormal movements            | Abnormal movements                            |
| 10,2%                        | 16,1%                                        |
| Headache                      | Headache                                      |
| 9,8%                         | 12,9%                                        |
| Postural instability or falls | Postural instability or falls                  |
| 8,5%                         | 16,1%                                        |
| Swallowing difficulties       | Swallowing difficulties                        |
| 6,1%                         | 12,9%                                        |
|                               | **BCRSS 2 (n=77)**                            |
| Fatigue                      | Fatigue                                      |
| 31,2%                        | 30,4%                                        |
| Memory complaints             | Memory complaints                             |
| 20,8%                        | 33,9%                                        |
| Sleep disorders              | Sleep disorders                              |
| 19,5%                        | 44,6%                                        |
| Myalgia                      | Myalgia                                      |
| 24,7%                        | 32,1%                                        |
| Depressive symptoms/anxiety  | Depressive symptoms/anxiety                   |
| 20,8%                        | 32,1%                                        |
| Loss of dependency in IADL   | Loss of dependency in IADL                    |
| 24,7%                        | 33,9%                                        |
| Blurring/loss of vision       | Blurring/loss of vision                       |
| 19,5%                        | 12,5%                                        |
| Numbness/tingling             | Numbness/tingling                             |
| 15,6%                        | 16,0%                                        |
| Hyposmia/hypogeusia           | Hyposmia/hypogeusia                           |
| 15,6%                        | 12,5%                                        |
| Urinary dysfunction           | Urinary dysfunction                           |
| 9,1%                         | 12,5%                                        |
| Confusion/Dizziness           | Confusion/Dizziness                           |
| 11,7%                        | 12,5%                                        |
| Dizziness/Hypotension         | Dizziness/Hypotension                         |
| 11,7%                        | 14,3%                                        |
| Gait disturbances             | Gait disturbances                             |
| 7,8%                         | 17,9%                                        |
| Abnormal movements            | Abnormal movements                            |
| 6,5%                         | 14,3%                                        |
| Headache                      | Headache                                      |
| 6,5%                         | 12,5%                                        |
| Postural instability or falls | Postural instability or falls                  |
| 6,5%                         | 12,5%                                        |
| Swallowing difficulties       | Swallowing difficulties                        |
| 6,5%                         | 7,1%                                         |
|                               | **BCRSS 1 (n=57)**                            |
| Fatigue                      | Fatigue                                      |
| 33,9%                        | 30,4%                                        |
| Memory complaints             | Memory complaints                             |
| 44,6%                        | 33,9%                                        |
| Sleep disorders              | Sleep disorders                              |
| 32,1%                        | 44,6%                                        |
| Myalgia                      | Myalgia                                      |
| 32,1%                        | 32,1%                                        |
| Depressive symptoms/anxiety  | Depressive symptoms/anxiety                   |
| 33,9%                        | 33,9%                                        |
| Loss of dependency in IADL   | Loss of dependency in IADL                    |
| 29,4%                        | 29,4%                                        |
| Blurring/loss of vision       | Blurring/loss of vision                       |
| 21,4%                        | 21,4%                                        |
| Numbness/tingling             | Numbness/tingling                             |
| 12,5%                        | 12,5%                                        |
| Hyposmia/hypogeusia           | Hyposmia/hypogeusia                           |
| 12,5%                        | 12,5%                                        |
| Urinary dysfunction           | Urinary dysfunction                           |
| 16,0%                        | 16,0%                                        |
| Confusion/Dizziness           | Confusion/Dizziness                           |
| 12,5%                        | 12,5%                                        |
| Dizziness/Hypotension         | Dizziness/Hypotension                         |
| 17,9%                        | 17,9%                                        |
| Gait disturbances             | Gait disturbances                             |
| 14,3%                        | 17,9%                                        |
| Abnormal movements            | Abnormal movements                            |
| 12,5%                        | 17,9%                                        |
| Headache                      | Headache                                      |
| 12,5%                        | 7,1%                                         |
| Postural instability or falls | Postural instability or falls                  |
| 7,1%                         | 7,1%                                         |
| Swallowing difficulties       | Swallowing difficulties                        |
| 7,1%                         | 7,1%                                         |
**Table 1** Demographic and clinical characteristics of the sample according to COVID-19 severity. In bold significant results after Bonferroni correction * significant for the comparison between BCRSS1 vs BCRSS2 groups #: significant for the comparison between BCRSS2 vs BCRSS3 groups ¶: significant for the comparison between BCRSS1 vs BCRSS3 groups

**Abbreviations:** BCRSS, Brescia-COVID Respiratory Severity Scale; CIRS, Cumulative Illness rating scale; qSOFA, quick Sequential Organ Failure Assessment.

|                    | Total (n=165) | BCRSS 1 (n=57) | BCRSS 2 (n=77) | BCRSS 3 (n=31) | p value |
|--------------------|---------------|----------------|----------------|----------------|---------|
| Age, years         |               |                |                |                | 0.06    |
| Sex, female n (%)  |               |                |                |                | 0.16    |
| Days of Hospitalization |            |                |                |                | 0.001# ¶* |
| Oxygen therapy, n (%) |             |                |                |                | 0.001¶ |
| Non-invasive ventilation, n (%) |       |                |                |                | 0.001¶ |
| Intubation, n (%)   |               |                |                |                | 0.001# ¶ |
| qSOFA              | 0.44 ± 0.53   | 0.0 ± 0.0      | 0.48 ± 0.50    | 1.10 ± 0.29    | 0.001# ¶* |
| CIRS total         | 18.6 ± 3.3    | 18.1 ± 3.2     | 19.4 ± 3.6     | 17.9 ± 2.8     | 0.03    |
| CIRS, severity mean| 1.35 ± 0.25   | 1.31 ± 0.24    | 1.40 ± 0.26    | 1.28 ± 0.20    | 0.02    |
| CIRS, total hospitalisation |       | 22.1 ± 3.6    | 21.6 ± 3.6    | 22.4 ± 3.5    | 0.32    |
| CIRS, severity mean hospitalisation |        | 1.70 ± 0.28   | 1.65 ± 0.28   | 1.73 ± 0.27   | 0.32    |
| Patients reporting neurological symptoms |     | 120 (72.7%) | 42 (73%) | 52 (68%) | 26 (84%) | 0.07    |
| Number of neurological symptoms reported |     | 2.76 ± 3.03 | 3.00 ± 2.83 | 2.1 ± 2.52 | 4.1 ± 3.96 | 0.004# |
| Neurological examination (n=105) |       |                |                |                |        |
| Neurological abnormalities at examination |       | 42/105 (40%) | 11/37 (29.7%) | 22/45 (48%) | 9/23 (39%) | 0.12    |
| Hyposmia/hypogeusia |       | 19/105 (18%)  | 6/37 (16.2%)  | 7/45 (15.0%)  | 6/23 (26%) | 0.51    |
| Cognitive deficits |       | 17/105 (16%)  | 1/37 (2.7%)   | 12/45 (26%)   | 4/23 (17.4) | 0.01    |
| Tremor             |       | 13/105 (12%)  | 4/37 (10.8%)  | 6/45 (13.3%)  | 3/23 (13.0%) | 0.89    |
| Low-limb hypoesthesia |       | 6/105 (5.7%)  | 2/37 (5.4%)   | 2/45 (4.4%)   | 2/23 (8.6%) | 0.80    |
| Motor Deficits     |       | 2/105 (1.9%)  | 1/37 (2.7%)   | 1/45 (2.2%)   | 0/23 (0%)   | 0.87    |