Medical and Research Publications
International Open Access

**Research Article** **Journal of MAR Pulmonology (Volume 3 Issue 4)**

# Three– month outpatient follow-up of discharged COVID – 19 patients: a single center cross – sectional study

T. Aloè[1], L. Benedetti [2,3], S. Garbarino[11], E. Tagliabue[1], A. Torricella[5], C. Campi[11] , M. Piana[4], M. Grosso[1], S.G. Grisanti[3], C. Sepulcri[6], F. Cosini[7], F. Baldi[6], D.Giacobbe[6], A. Sulli[9], D.Ferone[8], M. Bassetti[6], L. Castellan[5], M. Amore[9] and E. Barisione[1]

1. Interventional Pulmonology Unit, Policlinic San Martino University Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy

2. Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy

3. Division of Neurology, Policlinic San Martino University Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy

4. LISCOMP, Department of Mathematical Sciences, University of Genoa and CNR - SPIN Genoa, Italy

5. Department of Radiology, Policlinic San Martino University Hospital, IRCCS for Oncology and Neuroscience, University of Genoa, Italy

6. Infectious Diseases Unit, Policlinic San Martino University Hospital, IRCCS for Oncology and Neuroscience, university of Genoa, Italy

7. Allergy and Respiratory Diseases, Policlinic San Martino University Hospital, IRCCS for Oncology and Neuroscience, University of Genoa, Italy

8. Endocrinology Unit, Department of Internal Medicine, Policlinic San Martino University Hospital, IRCCS for Oncology and Neuroscience, University of Genoa, Italy

9. Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy

10. Research Laboratories and Clinical Division of Rheumatology, Department of Internal Medicine, University of Genova, IRCCS AOU San Martino, Genova, Italy.

11. LISCOMP, Department of Mathematical Sciences, University of Genoa, Genoa, Italy

**Corresponding Author: Dr. T. Aloè,** Interventional Pulmonology Unit, Policlinic San Martino University Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy.



**Received Date: August 05, 2021**

**Published date: September 01, 2021**

***Abstract***

***Background:*** *Despite the growing literature describing the clinical and radiologic progression of COVID-19 and the course of its acute phase, little is known about the post-acute patients' condition and, since COVID-19 is a new disease, about the possible long-term health consequences.*

***Purpose:*** *The objective of this paper is to describe the clinical characteristics of COVID-19 survivors at three-month follow-up after the acute phase and identify potential risk factors associated with persistent abnormalities.*

***Materials and Methods:*** *Between July and November 2020, for this single center cross – sectional study 148 patients (85 [57%] men; mean age, 63 range 31- 85 years) were enrolled. In this cohort the severity of COVID 19 acute course was mild for 20% of patient; moderate for 33%; mild – severe for 22%; severe for 25%. The average length of hospital stay was 26 days (range 3 – 111). The most commonly recovery complication was overlapping infection (18%), followed by thrombotic events (9% pulmonary, 8% other district), hematoma (6%), kidney failure (4%) and cardiac impairment (4%). Patients' post COVID-19 evaluation was performed averagely 12 weeks after the acute phase (range 10 – 15 weeks) through standardized sets of questionnaires (core components included demographic data, body mass index comorbidities, acute phase COVID 19 course and data about post COVID 19 manifestations) and clinical investigations. Chest radiological study, pulmonary function tests and diffusion capacity for carbon monoxide (DLCO), 6 minutes walking test laboratory analysis, echocardiogram and, if necessary, a specialist assessment were collected. Multivariable logistic regression was used*

hospitalization, and long-term health consequences.

**Results:** Analysis revealed that at the three months evaluation a large percentage **(**67%**)** of subjects still suffered from several multiorgan symptoms. The most common persistent symptoms were fatigue, effort dyspnoea followed by hair loss and psychological impairment. Pulmonary radiological and functional studies showed persistent abnormalities in 54% and 28% respectively, although these percentages fall to 30% if we consider severe radiological impairment **(**> 5%**)** and to 3% for severe decreased pulmonary diffusion capacity for carbon monoxide. 6-minute walk test resulted pathological for desaturation in 14% of cases. Multivariable analysis identified an higher number of onset symptom during acute phase as independent predictors for many persistent symptoms at 3 months: fatigue **(**odds ratio [OR]: 1.08, 95%CI:1.02-1.14, p=0.006**)**, dyspnoea **(**odds ratio: 1.05, 95%CI:1.01-1.09, p=0.02**)**, hair loss **(**odds ratio: 1.01, 95%CI:1.00-1.02, p=0.03**)** and psychological impairment **(**odds ratio: 1.05, 95%CI:1.01- 1.09, p=0.02**)**. In addition, the model showed that developed neurological **(**odds ratio: 1.16, 95%CI:0.91-1.45, p=0.01**)** or infective **(**odds ratio: 0.99, 95%CI:0.83-1.18, p=0.01**)** complications during hospitalization were risk factors for persistent neurological symptoms.

**Conclusions:** The results of this single center cross-sectional study imply that COVID-19 may result in a long-lasting syndrome, with residual symptoms **(**fatigue, dyspnoea, hair loss and psychological impairment**)** associated with a high number of onset symptoms during the disease acute phase. Since the SARS CoV2 infection causes an elevated cytokine release and immune-cell hyperactivation, immune dysregulation and multisystem inflammatory syndrome could be involved in this persistence of post infection symptoms. Our analysis showed that developed neurological or infective complications during hospitalization were risk factors for persistent neurological symptoms. This result can be explained by the fact that, during acute phase, there are different mechanisms by which SARS-Cov-2 may enter and damage the nervous system **(**direct infection injury, blood circulation pathway, neuronal pathway, immune mediated injury, hypoxic injury**)**. Further, critical illness polyneuropathy **(**CIP**)** is a frequent condition in critically ill patients that recognized sepsis among the most significant risk factor.

Finally, in our opinion management of COVID-19 survivors should be optimized through a multidisciplinary approach and, although further studies result necessary, optimise the management during acute phase in order to prevent complications could reduce long term sequela.

## Introduction

At the end of 2019 a novel coronavirus (SARS CoV2) arose in Wuhan China and caused a significant global medical issue, with a growing number of cumulative confirmed cases (1,2). The clinical spectrum of the SARS CoV2 infection (COVID-19 from now on) ranges from mild respiratory symptoms to severe multiorgan disease (3). The occurrence of such a wide spectrum of diagnostic and clinical events is probably the main lesson learnt from the first wave of the COVID-19 contagion, as extensively described and discussed in an impressive amount of recently published scientific literature (4–10). However, with the progression of the pandemic, several evidences, often of multi- organ character, are emerging about clinical symptoms and complications that may persist for several months after hospitalization. These evidences show that COVID-19 survivors often present persistent health issues that include cough and breathing difficulties, enduring fatigue, and issues that can be associated to post-traumatic stress disorders.

According to the NICE guidelines on long COVID-19 the two definitions of post-acute COVID-19 include ongoing symptomatic COVID-19 (symptoms between 4 and 12 weeks after the start of acute symptoms) and post-COVID-19 syndrome (symptoms for more than 12 weeks after the start of acute disease) (11). In the last few months, several observational studies contributed to a better refinement of these definitions, thus allowing a more sophisticated characterization of long COVID-19 (12–14). However, very few papers so far have been published about the identification of descriptors of the acute COVID-19 phase that may significantly impact on post disease manifestations.

In particular, a very recent study has been conducted on a population of around 4,000 individuals who utilized a specifically designed app in order to self-report their long COVID-19 symptoms. This analysis pointed out a statistically significant correlation between the number of symptoms in the acute phase with typical long COVID-19 manifestations. Using more detailed information acquired from standardized questionnaires and clinical investigation, the present study confirms this correlation, and, further, proves that neurological and infective complications during hospitalization are risk factors for neurological complications at 12 weeks after the acute phase.

## Methods

### Population overview

The present observational, cross sectional study was conducted at the IRCCS Ospedale Policlinico San Martino in Genoa (Italy), from July 2020 to November 2020. Patients were referred to the post COVID-19 evaluation either by their general physician or directly, in case they were discharged from a COVID-19 hospital unit from March 2020 to July 2020. The service delivery model followed established clinical criteria as for traditional outpatient programs. Therefore, patients with active neoplastic disease and patients with severe comorbidities (such as psychotic disorder, dementia or who were unable to move freely due to concomitant osteoarthropathy disease) not allowing outpatient medical examination were excluded from the study. The study involved 148 subjects with previous SARS CoV 2 infection, 63 (43%) of them being females and 85 (57%) males. Median age was 62 years (range 31 – 85). Complete demographic, baseline characteristics and comorbidities data are reported in Table 1.

### COVID-19 diagnosis and acute phase

Acute phase was defined as the time between symptom onset and hospital discharge.

The severity of the COVID 19 acute phase course was divided into four categories: the first group included the mild cases, not requiring oxygen supplemental; the second group included the moderate cases, receiving oxygen therapy; the third group included the mild-severe cases, requiring continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) support; the fourth group included the severe cases, requiring orotracheal intubation and intensive care unit (ICU) admission.

COVID-19 diagnosis was made by relying on laboratory assessment, either by molecular assays on nasopharyngeal swab (92%) or by molecular assays on bronchoalveolar lavage (1%) or in case of patients with clinical and radiological lesions strongly suggestive for SARS CoV2 infection (7%). Severity of COVID 19 course was mild for 20% of patient; moderate for 33%; mild – severe for 22%; severe for 25%. The average length of hospital stay was 26 days (range 3 – 111); 14% of patients had never been hospitalized but had received home care treatments. The most common recovery complication was overlapping infection (18%), followed by thrombotic events (9% pulmonary, 8% other district), hematoma (6%) (mainly iliopsoas muscle was involved – probably due to enoxaparin treatment), kidney failure (4%), and cardiac impairment (4%) (15,16). At hospital discharge, 4% of patients needed to continue supplemental oxygen therapy, but none of them had chronic respiratory failure in their personal anamnesis. Principal characteristics about acute phase course are reported in Table 2.

**Data collection**

For each patient, the cross-sectional post-discharge evaluation was performed averagely 12 weeks after acute phase of COVID 19 **(**range 10 – 15 weeks**)** via standardized sets of questionnaires and investigations. The core components included patients' assessment via standard questionnaire to evaluate demographic data **(**age, gender, smoking**)**, body mass index **(**BMI**)** comorbidities, acute phase COVID-19 course **(**onset symptoms, severity of the disease, therapy, complications, duration of the hospitalization, hospitalization time and time interval for having two subsequent COVID 19 swabs with negative result**)** and data about post COVID-19 manifestations **(**residual symptoms such as fatigue, dyspnoea, hair loss, neurological symptoms, chest pain**)**. Dyspnoea was investigated by means of the Medical Research Council **(**mMRC**)** questionnaire. The mMRC scale is a validated self-reported questionnaire to characterize the level of dyspnoea with physical activity in which higher scores correspond with increased dyspnoea.

At follow up program intake, patients underwent a full medical assessment including full pulmonary function tests, 6-minute walking test, either a high-resolution computed tomography **(**CT**)** or an X ray of the chest, laboratory analysis, echocardiogram and, if necessary, a specialist assessment **(**cardiological, neurological, psychiatric, etc**)**.

Imaging evaluation at three months was performed with high resolution CT or contrast-enhanced CT. High resolution CT **(**HRCT**)** was performed on a multidetector 16 row CT scanner with volumetric acquisition during a single full inspiration; 1,25 mm contiguous thin slices were reconstructed with standard and high-resolution filters for evaluation. Patients complicated by pulmonary thromboembolism during the acute phase or by abdominal haematoma were evaluated by contrast-enhanced CT scan in order to evaluate pulmonary reperfusion or hematoma evolution.

When available, the chest CT images performed during the hospital stay and the follow – up images were compared. The CT features were evaluated by one experienced radiologist and one pneumologist. A Six-Minute-Walk Test **(**6MWT**)** was performed during outpatient first assessment, considering as pathological an arterial oxygen saturation value below 90%. Those patients who presented physical contraindications to the 6MWT were excluded. Spirometry and lung volumes were measured with the subject sitting in whole – body plethysmograph. Forced vital capacity **(**FVC**)**, forced expiratory volume in one second **(**FEV1**)**, FEV1/FVC ratio, total lung capacity **(**TLC**)**, standard diffusion lung capacity for carbon monoxide **(**DLCO**)** were determined following standard procedures and compared with available predicted values **(**17,18**)**.

Since acute phase of COVID-19 is considered as a multiorgan disease, laboratory tests were performed at tree months revaluation in order to exclude persistent systemic infection or treatment related to other acute exacerbation of chronic disease. Blood tests included blood count, kidney, liver and thyroid functions, ions, LDH, PCR, B-type natriuretic peptide, glycated haemoglobins, d-dimer.

Blood gas analysis was performed to measure the levels of oxygen and carbon dioxide concentrations in the blood and to evaluate persistency of respiratory insufficiency.

### Regression analysis

We performed a multivariate logistic linear regression analysis to investigate the impact of both demographic and clinical data, and COVID-19 severity and hospitalization, on the post COVID-19 symptoms at three months follow-up. We considered:

• Whether the variable we defined to account for the severity of COVID-19 during the acute phase **(**four stages: mild, moderate, mild-severe, severe**)** could be considered as a valid and robust measure of the severity of acute COVID-19. To do so, we performed a linear regression analysis predicting such variable from demographic and clinical data; specifically: sex, BMI, age, smoking habit and number of comorbidities at onset.

• The impact of both demographic and clinical data, and COVID-19 severity and hospitalization, on the post COVID- 19 symptoms at three months. Specifically, we built a linear regression model to predict the five most common symptoms **(**fatigue, anxiety, hair loss, dyspnoea, neurological impairment**)** from a set of variables including both demographic and clinical **(**sex, BMI, age, smoking habit, number of comorbidities at onset**)**, and COVID-19 severity and hospitalization **(**number of COVID-19 symptoms at inset, thoracic X-ray scan severity, severity of COVID-19 at onset, cardiological complications, infective complications, TEP complications, neurological complications**)**.

## Results

### Major post COVID 19 clinical manifestations

Analysis of post COVID 19 manifestations revealed that at the three months revaluation a large percentage of subjects still suffered from several multiorgan symptoms. In our cohort, only 33% of patients evaluated at three months from post-acute phase claimed no residual symptoms. It is worth mentioning that some patients reported hair loss as the only symptom **(**18.9%**)**. As shown in Table 3, the most common reported symptoms were fatigue and dyspnoea followed by hair loss and phycological impact. Approximately 80% of the subjects who reported symptoms, reported persistence of one or two

symptoms, while only few of them **(**18%**)** reported more than two symptoms. Complete overview of symptoms is provided in Table 3.

| BMI | N (%) |
|---|---|
| Normal weight (18 - 25) | 76 (52%) |
| Over weight (25,1 - 29,9) | 54 (36%) |
| Obesity (> 30) | 18 (12%) |
| **GENDER** | **N (%)** |
| Male | 85 (57%) |
| Female | 63 (43%) |
| **SMOKING** | **N (%)** |
| Smoker | 8 (6%) |
| Former smoker | 66 (46%) |
| No smoke | 74 (48%) |

| COMORBIDITIES | N (%) |
|---|---|
| Hypertensive disease | 79 (53%) |
| Dyslipidaemia | 30 (20%) |
| Diabetes | 17 (11%) |
| Bronchial asthma | 14 (8%) |
| Heart disease | 12 (8%) |
| Neoplasm in FU | 13 (8%) |
| Gastritis/GERD | 12 (8%) |
| Heart failure | 12 (8%) |
| Thyroiditis | 11 (7%) |
| Autoimmune disease | 9 (6%) |
| Hepatopathy | 7 (5%) |
| Neoplasm in treatment | 6 (4%) |
| COPD | 2 (1%) |
| Chronic kidney disease | 2 (1%) |
| Organ transplant | 0 (0%) |
| Normal weight (18 - 25) | 76 (52%) |
| Over weight (25,1 - 29,9) | 54 (36%) |
| Obesity (> 30) | 18 (12%) |
| **GENDER** | **N (%)** |
| Male | 85 (57%) |
| Female | 63 (43%) |
| **SMOKING** | **N (%)** |
| Smoker | 8 (6%) |
| Former smoker | 66 (46%) |
| No smoke | 74 (48%) |

| COMORBIDITIES | N (%) |
|---|---|
| Hypertensive disease | 79 (53%) |
| Dyslipidaemia | 30 (20%) |
| Diabetes | 17 (11%) |
| Bronchial asthma | 14 (8%) |
| Heart disease | 12 (8%) |
| Neoplasm in FU | 13 (8%) |
| Gastritis/GERD | 12 (8%) |
| Heart failure | 12 (8%) |
| Thyroiditis | 11 (7%) |
| Autoimmune disease | 9 (6%) |
| Hepatopathy | 7 (5%) |
| Neoplasm in treatment | 6 (4%) |
| COPD | 2 (1%) |
| Chronic kidney disease | 2 (1%) |
| Organ transplant | 0 (0%) |

**Table 1**: Baseline characteristics of the study population, severity course. GERD= gastroesophageal reflux disease; COPD= Chronic Obstructive Pulmonary Disease, FU= follow up.

| CARE SETTING | N (%) |
|---|---|
| Hospitalization | 128 (86%) |
| Home care | 20 (14%) |
| **DIAGNOSIS** | **N (%)** |
| nasopharyngeal swab | 136 (92%) |
| bronchoalveolar lavage | 2 (1%) |
| clinical and radiological lesions strongly suggestive | 10 (7%) |
| **SEVERITY COURSE** | **N (%)** |
| Mild severity | 30 (20%) |
| Moderate severity | 48 (33%) |
| Mild – Severe | 33 (22%) |
| Severe | 37 (25%) |
| **TREATMENT RECEIVED DURING** | **N (%)** |

| ACUTE PHASE | |
|---|---|
| Corticosteroids | 106 (72%) |
| Duronavir- Ritonavir | 44 (30%) |
| Oseltamivir | 21 (14%) |
| Remdesivir | 5 (3%) |
| Anakinra | 2 (1%) |
| Intravenus immunoglobulin | 8 (5%) |
| Hydroxychloroquine | 103 (70%) |
| Antibiotics | 126 (85%) |
| Enoxaeparin sodium | 113 (76%) |
| **RECOVERY COMPLICATIONS** | **N (%)** |
| Overlapping infection | 27 (18%) |
| Thrombotic events: | |
| Pulmonary thrombosis | 13 (9%) |
| Other district | 12 (8%) |
| Hematoma | 9 (6%) |
| Kidney failure | 6 (4%) |
| Cardiac impairment | 6 (4%) |
| OTHER | |
| Time from symptom onset to diagnosis, days | 7 (0 – 42) |
| Length of hospital stay, days | 26 days (range 3 – 111) |
| Number onset symptom | 3 (range 0 – 9) |
| Necessity of oxygen therapy at discharge | 6 (4%) |

**Table 2:** characteristics of acute phase

| SYMPTOMS | TOTAL NUMBER | % |
|---|---|---|
| Fatigue | 42 | 28.4 |
| Dyspnoea | 36 | 24.3 |
| Hair loss | 28 | 18.9 |
| Psychological impact | 20 | 14.0 |
| Neurological impairment | 15 | 10.0 |
| Chest pain | 10 | 6.8 |
| Cough | 10 | 6.8 |
| Ageusia | 9 | 6.7 |
| Anosmia | 9 | 6.7 |
| Arthralgia | 8 | 5.4 |
| Myalgia | 4 | 2.7 |
| Erectile dysfunction | 2 | 1.4 |
| Tachycardia | 2 | 1.4 |
| Headache | 1 | 0.7 |

**Table 3**: Overview of the reported symptoms at 3 months evaluation for the 148 study cohort.

The most common symptom was fatigue (29%), defined by impaired exercise tolerance, reduced capacity and/or impaired memory and concentration.

The second most common symptom was dyspnoea (24%). Most people affected by this symptom (99%) reported its manifestation in case of physical effort (mMRC < grade 5). Among other symptoms, hair loss was reported by 28 patients (23/28 females and 5/28 males). Begin of effluvium was noted in hospitalized patients, either during hospitalization or close to the discharge date. None of subjects claiming hair loss reported other associated symptoms as scalp itchiness, skin desquamation or hair loss in other body areas. The examination detected diffuse non-scarring hair loss in all the study subjects.

Approximately 14% of patients enrolled in study reported persistence of moderate to severe anxiety symptoms, or depressive symptoms, at three-month follow-up, whereas a lower percent of cases (< 1%) experienced symptoms corresponding to post traumatic stress disorder (PTSD). Moreover, 14% of these patients reported chronic history of psychiatric disease.

One of the most common neurological symptoms is hyposmia/anosmia, often associated to taste impairment (19). Among patients included in our study, 18% reported smell and/or taste impairment as onset symptoms and 39% of these patients complained persistence of these alterations. Interestingly, a significant number of patients who recovered smell/taste reported a transient period when smell and/or taste were altered (parosmia/dysgeusia, i.e. things do not smell/taste like they used to) before full recovery. The most common scent reported were burnt, coffee or mold taste, often associated with salty or bitter taste.

Furthermore, a few percentages (10%) of our patients reported other persistent neurological symptoms: the most common were headache and dizziness, followed by impairment of cranial or peripheral nerves.

At least, approximately 40% of population in study reported cognitive disturbances, especially memory disorders and attention deficit.

Only a small proportion of patients reported persistent myalgia and arthralgia (5%). Arthralgia is a common symptom that occurs in patients during acute phase of COVID-19. However, to date information on rheumatic and inflammatory manifestations (such as arthritis) are scarce in literature. Patients included in this study reported sudden onset of polyarticular pain after initial illness phase. At three months revaluation shoulder and hand joints were mainly affected; no patient reported rheumatic diseases in their medical history.

**Specialist evaluations at three months**

**Radiology and pulmonary function**

In our cohort, approximately 54% of cases showed radiological abnormalities consistent with extended ground glass area **(**GGOs**)**, consolidation or fibrosis, whereas the remaining cases had complete resolution of the initial alterations, limited GGOs area, or only residual fibrous stripes. The main residual lesions were ground glass area **(**46%**)**, fibrotic stripes **(**31%**) (**in this group 36% showed bronchiectasis**)**. Only in a minimal percentage of cases **(**<1%**)** residual CT pattern showed consolidation **(**Figure 1**)**

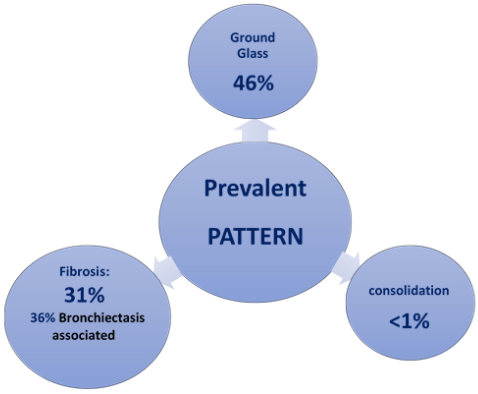


**Figure 1:** prevalent CT scan pattern at 3 months evaluation.

Exams performed in this study were compared to an acute phase radiological study when available; all exams showed an improvement in imaging findings including reduction in number and size, or even resolution, of GGOs, decrease in the consolidation density with gradual reduction in the density and transition to ground glass opacity and, finally, in a few percentage **(**<5%**)** of cases resolution of fibrosis displayed by the previous test. **(**20**)**.

At three month evaluation a contrast enhanced CT scan were performed in patients **(**9%**)** complicated by pulmonary embolism during acute phase of COVID-19. All exams showed complete resolution of massive or micro thromboembolism.

**Pulmonary functional tests**

In our cohort after three months from acute phase, 28% of patients had decreased pulmonary diffusion capacity for carbon monoxide, 25% mild grade, 3% moderate – severe grade **(**scale according to ERS/ATS DLCO standards**)**. Approximately 85% of patients had a normal total lung capacity; in the rest of population, we observed 13% of mild restrictive ventilatory deficit **(**scale according to ERS standard. Airflow obstruction was present in less than 1% of our population and these patients had chronic obstructive lung pathology in their medical history.

**Six-Minute-Walk-Test**

A total of 135 out of 148 patients completed the test and few patients **(**9%**)** were excluded due to their physical condition. The median distance covered during the examination was 455 m **(**range 220 – 580 m**)**, an abnormal desaturation during physical exercise was present in 14% of cases.

All patients with 6MWT abnormalities presented an altered functional pulmonary test and/or persistent lesions at the imaging. **(**14**)**

**Blood test**

Blood tests included blood count, kidney, liver and thyroid functions, ions, LDH, PCR, B-type natriuretic peptide, glycated haemoglobins, d-dimer. Results showed no significant persistent abnormalities, except for three patients who developed renal failure during acute phase of illness which was still present at three-month control.

The majority of patients refused the blood gas analysis and for this reason only 50 arterial blood draws were collected; in available samples no abnormalities were recorded. In our cohort, six patients were discharged with the recommendation of long-term oxygen therapy and at three-month revaluation only one patient needed a prolonged prescription for oxygen due to persistent desaturation during physical exercise.

**Echocardiogram**

A small percentage **(**4%**)** of survived patients in study cohort, during hospital recovery, presented cardiovascular complications. At three-month evaluation, results showed approximately 3% of persistent pericardial effusion in the major cases with no associated constrictive physiology. In only two cases, moderate grade of pericardial effusion persisted. Both patients developed viral myocarditis during acute phase of COVID-19. During the post-acute phase, no other effects of SARS-CoV-2 infection on the heart were identified in the study population, except for one case of pulmonary hypertension associated with interstitial lung disease.

**Statistical results**

We performed a multivariate linear logistic regression analysis to investigate the impact of both demographic and clinical data, and COVID 19 severity and hospitalization, on the post COVID-19 symptoms at three months. We found that:

• Both sex **(**M**)** and BMI showed significant correlation with the variable we defined to account for the severity of COVID 19 **(**sex: p=0.003; BMI: p=0.0003**)**, which agrees with recent results and guarantees that such variable is a valid measure of COVID-19 severity. **(**1**)**

• Significant statistical correlation between number of symptoms of COVID 19 acute phase and persistent fatigue **(**odds ratio [OR]: 1.08, 95% CI:1.02-1.14, p=0.006**)**, effort dyspnoea **(**OR: 1.05, 95%CI:1.01-1.09, p=0.02**)**, hair loss **(**OR: 1.01, 95% CI:1.00-1.02, p=0.03**)** and psychological impairment **(**OR:1.05,95%CI:1.01-1.09,p=0.02**)**. In addition, the model showed that developed neurological **(**OR: 1.16,95%CI:0.91-1.45,p=0.01**)** or infective **(**OR:0.99,95%CI:0.83-1.18, p=0.01**)** complications during.

hospitalization were risk factors for persistent neurological symptoms. No other significant statistical correlation was found considering other variables analysed **(**demographic data, comorbidities, severity course of the acute phase**)**. Illustration of these results is reported in Figure 2.

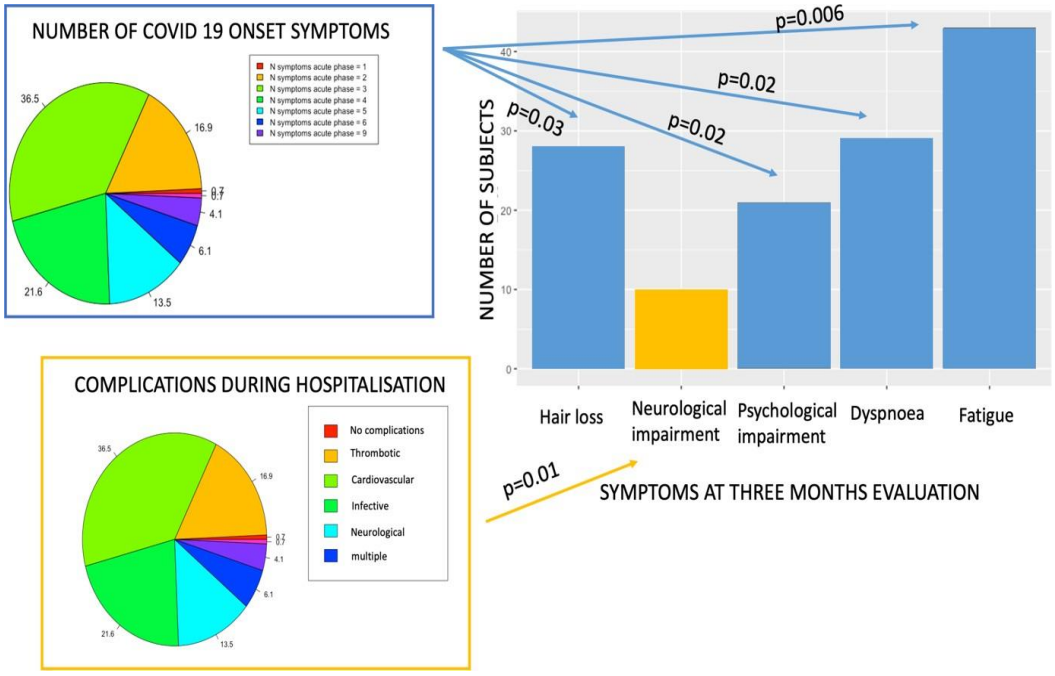


**Figure 2:** Correlation results between post COVID 19 symptoms and acute COVID 19 number of onset symptoms and complications during hospitalisation.

## Discussion

There are currently few publications on the follow-up of patients with COVID-19 **(**21,22**)**.

In these studies, the most commonly reported symptoms were fatigue, dyspnoea, hair loss, mental health impairment and, in a minority of cases, cardiological, neurological and rheumatic impairment. We first point out that, although cardiovascular impairment was described during the acute phase of COVID-19 **(**in our survivors' cohort, during hospital recovery, 4% presented cardiovascular complications**)**, there are no current data on long- term COVID-19 cardiovascular complications **(**23**)**.

Therefore, we decided to implement cardiac investigation just in those cases presenting cardiac impairment during acute phase. Furthermore, for analogous reasons blood gas analysis has not been included in the post COVID-19 routine laboratory assessment, although it is still recommended for patients with persistent respiratory failure criteria at the clinical assessment.

Our analysis of post COVID-19 manifestations revealed that, at three months revaluation, a large percentage **(**67%**)** of subjects still suffered from at least one persistent symptom and a significant subgroup **(**18%**)** suffered from several **(**> 2**)** multiorgan symptoms, implying that this disease may result in a long COVID-19 syndrome. On the one hand, long COVID-19 is not observed just among patients who had severe illness and were hospitalized. In fact, earlier data have not consistently shown any correlation between the development of the severity of long COVID-19 **(**defined as gravity of singular symptom, persistence of more than two symptoms or poor chest imaging outcome**)**, and the severity of the disease during the acute phase. Further, in our cohort multivariable logistic regression analysis showed a significant statistical correlation between number of onsets symptoms and persistent fatigue, effort dyspnoea, hair loss and psychological impairment at three months from acute illness recovery **(**no other significant statistical correlation was found considering the other variables analysed: demographic data, comorbidities, severity course of the acute phase**)**. This confirms the results obtained by Sudre et al. **(**24**)**

It is well-established that post intensive care syndrome, including chronic fatigue, physical, emotional, and cognitive impairments, is described at long term follow-up in patient recovering from critical illness or intensive care treatment **(**25**)**. However, it is also established that SARS CoV2 infection causes an elevated cytokine release and immune-cell hyperactivation that could evolve in a cytokine release syndrome **(**26**)**. This cytokine storm is characterized by constitutional symptoms, systemic inflammation and multiorgan dysfunction that can determine the persistence of post infection effects. In particular, recent studies have focused on inflammation as a cause of chronic fatigue **(**27**)**. Nevertheless, it is reasonable to consider that persistent fatigue among COVID-19 patients is not only related to the acute phase, but it is a multifactorial manifestation that is due to different causes such as weight loss during hospitalization, baseline performance status and physical condition. In all patients who claimed fatigue at three months evaluation, laboratory tests, including blood count, ionogram, cardiac **(**troponin and natriuretic peptide levels**)**, liver, kidney, and thyroid functions, were normal. Only two patients showed mild restrictive syndrome in pulmonary functional test, while few patients, reporting persistent fatigue, showed chest imaging abnormalities or cardiac impairment. In all remaining patients, i.e. the ones with no alteration in either imaging and functionality tests, physical deconditioning plays an important role.

The third most common symptom in the cohort **(**19%**)** was hair loss, the beginning of effluvium being noted either during hospitalization or close to discharge date. Excluding androgenetic alopecia, most common triggers for hair loss are iatrogenic cause, infective cause **(**e.g. tinea capitis, kerion**)** due to

systemic diseases (e.g. autoimmune diseases, endocrine diseases, etc.) and stress- correlated cause (28). Hair loss identified in the study population was primarily investigated focusing on iatrogenic and stress-correlated causes. Our data presented no correlation between either hair loss and acute phase treatment or stress-correlated reason; these symptoms were investigated as persistent psychogenic manifestation such as insomnia, anxiousness, depression, claimed by patients either during anamnesis process or after COVID-19, intensive care during hospitalization and duration for having complete recovery from COVID-19. Our analysis showed as well a strong correlation between hair loss and a high number of onset symptoms, in accordance with what reported by Shanshal in a case report that attributes the hair loss to the Covid-19 related anagen effluvium, possibly due to profound inflammatory insult accompanying the infection (29). Research on this subject is still scarce, additional studies being required to better understand the clinical features and mechanisms of post COVID hair loss pathogenesis such as hypoxia, vascular endothelial damage, immune disorder or nutritional deficiency.

At three months evaluation, in a significant number of cases (14%) patients endorsed psychological impact, the most common symptoms being anxiety, sleep difficulties and depression; in a smaller rate of case, patients experienced symptoms corresponding to post traumatic stress disorder.

Ho-Bun Lam and colleagues showed that many SARS (Severe acute respiratory syndrome) survivors developed psychiatric morbidity that persisted at 4 year follow up (30). In the specific case of COVID-19 an increased number of post-traumatic stress syndrome (PTSS) and depression was reported (31). Although COVID-19 may stress several systems of the body, including the brain, in the process of overcoming infection the direct effects of the virus and inflammatory or immune mediated response are not yet completely known. In our cohort, the strong association of persistent psychiatric disorders with a high number of onset symptoms could reflect an important role played by the inflammatory state. Depression, anxiety, and post-traumatic stress syndrome are, therefore, all potential long-term sequelae of COVID-19. For this reason, improved preventive measures and treatment of mental health imbalance, during acute illness and post COVID period are crucial.

Our study found that 10% of patients reported neurological alteration at three months evaluation, the main reported symptoms being headache, dizziness and either cranial or peripheral nerve impairment. Our analysis showed that the developed neurological and infective complications during hospitalization were risk factors for persistent neurological symptoms. As already known, many COVID-19 patients can develop neurological symptoms via different mechanisms (direct infection injury, blood circulation pathway, neuronal pathway, immune mediated injury, hypoxic injury). (32) In addition, critical illness polyneuropathy (CIP) is a frequent condition in critically ill patients. Even though the exact mechanism of axonal injury in CIP is unknown the most significant risk factors for the development of Intensive Care Unit Acquired Weakness (ICUAW) are sepsis, multiorgan dysfunction and acute respiratory distress syndrome (ARDS) conditions linked with SARS-CoV-2 infection complications (25). Similarly, many

studies have reported cognitive impairment, defined as “brain fog” in COVID-19 survivors. Memory alterations, as well as attention deficit have also been reported in our population **(**40%**)**.

At least approximately 14% of our patients reported olfactory and/or taste disorders during acute phase of COVID-19, this percentage dropping to 7% at three months evaluation. One of the proposed mechanisms of anosmia and hyposmia in COVID-19 patients is the potential viral dissemination and spread from the cribriform plate, which is nearby the olfactory bulb **(**32**)**. Gane & Parker proposed an alternative pathogenetic mechanism other olfactory neuron viral infection and destruction. In their study, these authors reported that ACE2 receptor, the targeting protein of SARS CoV2, is expressed mainly on sustentacular cells, which support the olfactory neurons. The inflammation affects first these cells, causing swelling and disfunction of the area, and only subsequently also the olfactory neurons. These evidences could explain why some patients recovered normal sense of smell in few weeks, compared to other cases presenting persistent sense alterations. In these latter cases the olfactory neurons probably may need longer time to regenerate from the supply of stem cells. Lastly, alteration of the sense of smell before full smell recovery could be associated with neuron regeneration, and the author concluded that many forms of smell loss are helped by “physiotherapy for the nose” exposing patients to a fixed set of odorants every day.

We finally point out that, currently, it is not known how long is required to COVID-19 survivors in order to return to their usual state of health and if persistent sequalae will be permanent. This study highlights the need for revaluation not only in recovered patients with critical ill, but in all subjects with previous COVID-19 which should undergo long term monitoring program. Therefore, in our opinion management of COVID-19 survivors should be optimized through a multidisciplinary approach. In addition, in the view of the physical deconditioning and social isolation caused by acute phase of SARS-CoV-2 infection, especially among patients who had severe illness, proper planning of physical and respiratory rehabilitation, as well as a psychological evaluation could reduce long term sequela.

## References

1. Lai C-C, Liu YH, Wang C-Y, Wang Y-H, Hsueh S-C, Yen M-Y, et al. “Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 **(**SARS-CoV-2**)**: Facts and myths”. J Microbiol Immunol Infect. 2020 Jun;53**(**3**)**:404–12.

2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. “Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study”. The Lancet. 2020 Feb;395**(**10223**)**:507–13.

3. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. “Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study”. BMJ. 2020 Mar 26;m1091.

4. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. "Predictors of COVID -19 severity: A literature review". Rev Med Virol. 2021 Jan;31**(**1**)**:1–10.

5. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. "Coronavirus disease 2019 **(**COVID-19**)**: A literature review. J Infect Public Health". 2020 May;13**(**5**)**:667–73.

6. Ng M-Y, Lee EYP, Yang J, Yang F, Li X, Wang H, et al. "Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review". Radiol Cardiothorac Imaging. 2020 Feb 1;2**(**1**)**:e200034.

7. Ahmad I, Rathore FA. "Neurological manifestations and complications of COVID-19: A literature review". J Clin Neurosci. 2020 Jul;77:8–12.

8. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. "Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis". J Infect. 2020 Aug;81**(**2**)**:e16– 25.

9. Kakodkar P, Kaka N, Baig M. "A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 **(**COVID-19**)**". Cureus [Internet]. 2020 Apr 6 [cited 2021 Jun 21]; Available from: https://www.cureus.com/articles/29670-a-comprehensive-literature-review-on-the-clinical-presentation-and-management- of-the-pandemic-coronavirus-disease-2019-covid-19

10. Wolff D, Nee S, Hickey NS, Marschollek M. "Risk factors for Covid-19 severity and fatality: a structured literature review". Infection. 2021 Feb;49**(**1**)**:15–28.

11. Venkatesan P. "NICE guideline on long COVID". Lancet Respir Med. 2021 Feb;9**(**2**)**:129.

12. Gorna R, MacDermott N, Rayner C, O'Hara M, Evans S, Agyen L, et al. "Long COVID guidelines need to reflect lived experience". The Lancet. 2021 Feb;397**(**10273**)**:455–7.

13. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, et al. "'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19". Thorax. 2021 Apr;76**(**4**)**:396–8.

14. Townsend L, Dowds J, O'Brien K, Sheill G, Dyer AH, O'Kelly B, et al. "Persistent Poor Health Post-COVID-19 Is Not Associated with Respiratory Complications or Initial Disease Severity". Ann Am Thorac Soc. 2021 Jan 8;AnnalsATS.202009- 1175OC.

15. Liu S, Mei C, Zou H, Chang X, Ye Z. "Iliopsoas hematoma associated with low-molecular-weight heparin use: A case report". SAGE Open Med Case Rep. 2020 Jan;8:2050313X2093168.

16. G. M, Angles SB, F. L, V. S. "Spontaneous haematoma of the iliac psoas muscle: a case report and review of the literature". Arch Orthop Trauma Surg. 2002 Feb 1;122**(**2**)**:109–11.

17. Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, et al. “Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians”. Eur Respir J. 2017 Sep;50**(**3**)**:1700010.

18. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. “Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations”. Eur Respir J. 2012 Dec;40**(6)**:1324–43.

19. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. “Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study”. Clin Infect Dis. 2020 Jul 28;71**(**15**)**:889– 90.

20. Grillo F, Barisione E, Ball L, Mastracci L, Fiocca R. “Lung fibrosis: an undervalued finding in COVID-19 pathological series”. Lancet Infect Dis. 2021 Apr;21**(**4**)**:e72.

21. Cortinovis M, Perico N, Remuzzi G. “Long-term follow- up of recovered patients with COVID-19”. The Lancet. 2021 Jan;397**(**10270**)**:173–5.

22. Sivan M, Taylor S. “NICE guideline on long covid. BMJ”. 2020 Dec 23;m4938.

23. Mitrani RD, Dabas N, Goldberger JJ. “COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors”. Heart Rhythm. 2020 Nov;17**(**11**)**:1984–90.

24. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. “Attributes and predictors of long COVID”. Nat Med. 2021 Apr;27**(**4**)**:626–31.

25. Shepherd S, Batra A, Lerner DP. “Review of Critical Illness Myopathy and Neuropathy. The Neurohospitalist”. 2017 Jan;7**(**1**)**:41–8.

26. Fajgenbaum DC, June CH. Cytokine Storm. Longo DL, editor. N Engl J Med. 2020 Dec 3;383**(**23**)**:2255–73.

27. O’Connor CM. COVID-19 Fatigue. JACC Heart Fail. 2020 Jul;8**(7)**:592–4.

28. Wolff H, Fischer TW, Blume-Peytavi U. “The Diagnosis and Treatment of Hair and Scalp Diseases”. Dtsch Aerzteblatt Online [Internet]. 2016 May 27 [cited 2021 May 10]; Available from: https://www.aerzteblatt.de/10.3238/arztebl.2016.0377

29. Rivetti N, Barruscotti S. “Management of telogen effluvium during the COVID-19 emergency: Psychological implications”. Dermatol Ther [Internet]. 2020 Jul [cited 2021 May 10];33**(4)**. Available from: https://onlinelibrary.wiley.com/doi/10.1111/dth.13648

30. Lam MH-B. “Mental Morbidities and Chronic Fatigue in Severe Acute Respiratory Syndrome Survivors: Long-term Follow-up”. Arch Intern Med. 2009 Dec 14;169**(**22**)**:2142.

31. Vindegaard N, Benros ME. “COVID-19 pandemic and mental health consequences: Systematic review of the current evidence”. Brain Behav Immun. 2020 Oct;89:531–42.

32. Chen X, Laurent S, Onur OA, Kleineberg NN, Fink GR, Schweitzer F, et al. “A systematic review of neurological symptoms and complications of COVID-19”. J Neurol. 2021 Feb;268**(**2**)**:392– 402.

Linkografia

A. S. Gane, J. Parker https://theconversation.com/coronavirus- scientists-uncover-why-some-people-lose-their-sense-of-smell- 138898