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Insights into Long COVID: Unraveling Risk Factors, Clinical Features, Radiological Findings, Functional Sequelae and Correlations: A Retrospective Cohort Study

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Clinical significance

- Long COVID is a chronic multisystem disease that causes various symptoms and affects both in-patients and out-patients.
- In more than half of long COVID patients, fibrosis or ground-glass opacities (GGO) persisted on chest CT, as well as pulmonary functions were altered
- Multidisciplinary approach should be used to manage long COVID.

Abstract

Background: The long-term symptomatology of COVID-19 has yet to be comprehensively described. The aim of the study was to describe persistent COVID-19 symptoms in a cohort of hospitalized and home-isolated patients.

Methods: A retrospective cohort study was conducted on long COVID patients. Long COVID symptoms were identified, and patients were divided into hospitalized (in-patients) and home-isolated (out-patients) as well as according to the number of symptoms. Patients were examined by a multydisciplinary medical team. Blood tests, high resolution chest computed tomography (CT), physical and infectious examination were performed. Finally, in-patients were evaluated at two time-points: on hospital admission (T0) and after three months from discharge (Tpost).

Results: Three hundred and sixty-four COVID-19 patients were enrolled. 82% of patients reported at least one or more symptoms. The most reported symptom was fatigue. Chest CT showed alteration in 76% of patients and pulmonary function alterations were observed in 44.7% of patients.

A higher risk of presenting at least one symptom was seen in patients treated with corticosteroid and a higher risk of presenting chest CT residual lesion was observed in hospitalized patients and in patients that received hydroxychloroquine treatment. Moreover, a higher risk of altered pulmonary function was observed in older patients.

Conclusion: Long-term sequelae are present in a remarkable number of long COVID patients and pose a new challenge to the healthcare system to identify long-lasting effects and improve patients' wellbeing. Multi-disciplinary teams are crucial to develop preventive measures, and clinical management strategies.

Introduction

Acute phase of COVID-19 has been exhaustively defined [1,2]. Although most patients recover within few weeks, others complain of persistent long-term symptoms [3,4]. Several terms have been used to describe these long persisting signs and symptoms[5,6]. The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) defined "ongoing symptomatic COVID-19″ persistent symptoms from 5 to 12 weeks and "post-COVID-19″ in the case of persistent symptoms after 12 weeks. A similar classification was proposed by the UK Scottish Intercollegiate Guidelines Network (SIGN), and the UK Royal College of General Practitioners (RCGP) [7,8]. However, nowadays it is collectively referred to as long COVID [9–11] as resulted by the WHO using the Delphi consensus-based methodology. The term "long COVID" was defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation [10]

Long COVID seems to be a multisystemic disease [12], whose common symptoms include fatigue, shortness of breath, and psychological and cognitive dysfunction, with a general impact on everyday quality of life [1,13–15]. Long COVID symptoms might be of new onset, following the initial recovery from COVID-19 acute phase, or persist since the initial illness [1,14]. A wide and country-specific variation in the prevalence of long COVID insurgence has been observed[12]. The WHO reported that 17 millions of people across the European region might have experienced long COVID during the first two pandemic years [9].

The exact mechanism responsible for long COVID remains elusive , however a putative pathophysiology of the disease has been outlined and several hypotheses have been proposed [16]. A possible involvement of the oxidative stress and inflammation that might lead to a weak immunological response and inappropriate viral eradication [17] as well as a sustained endotheliopathy were suggested. Cardiovascular abnormalities following SARS-CoV-2 infections were also described, with up to 40% of patients developing pericarditis or myocarditis [18]. Noticeably, approximately one-third of hospitalized patients with acute kidney injury during the acute phase of COVID-19, did not fully regain renal function [19].

In addition, after COVID-19 acute phase a possible persistence of SARS-CoV-2 RNA in the central nervous system (CNS), that might result in neuronal loss, has been observed [20]. Indeed, neurological changes were demonstrated and have been considered as a possible explanation for common neurological long COVID manifestations (neuro-long COVID) [21,22].

In this context, considerable attention has been given to research involving long COVID risk factors identification [23,24]. However, long COVID features have yet to be comprehensively described.

The aim of this study was to describe the prevalence of persistent symptoms after COVID-19 acute phase in a cohort of hospitalized and home-isolated patients from the first and second pandemic wave in the post-COVID clinic.

Materials and methods

Study design and settings

From March 2020 to March 2021, a single-center retrospective cohort study was conducted in COVID-19 patients hospitalized or home-isolated with a confirmed history of acute COVID-19. Hospitalization was dictated by clinical judgement, evaluating risk factors, clinical and radiological features and was not encompassed by a general protocol.

All patients were unvaccinated and were enrolled consecutively. <18 years, admission to residency of retirement/nursery homes and death were considered as exclusion criteria.

After three months since hospital discharge or negative result for SARS-CoV-2 RNA in nasopharyngeal swab, all patients were invited to the long COVID clinic. Medical examination was performed by a multidisciplinary medical team. Specifically, blood tests, high-resolution chest computed tomography (CT), physical and infectious examination were performed in a single day visit. Moreover, the evaluation of Lung Function Testing (LFT) and 6 Minute Walking Test (6MWT) was performed at the long COVID visit (Tpost) (Figure 1).

The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Clinical feature and data collection on long COVID symptoms in study population

Long COVID symptoms have been defined according to the WHO definition [9]

Lung functions were quantified by spirometry, diffusing capacity or transfer factor of the lung for carbon monoxide (D_{LCO}), and a 6-minute walk test (6MWT) according to recommended guidelines were performed for the first time at the long COVID clinic, as well as chest CT [25]. Chest tomography (CT) scanners (Siemens Healthineers, Germany) were used for all examinations [26]. Specifically, lung parenchymal imaging findings were examined according to the standard glossary for thoracic imaging reported by Fleischner Society[27]. Two different pattern was used to describe the nature of abnormalities reported in the chest CT: pattern 1 indicated fibrosis, pattern 2 referred to ground glass opacities. In all cases, a previously described semi-quantitative CT severity scoring was calculated per each of the 5 lobes [28,29].

Overall, patients were stratified into two groups: in-patients, including those who were hospitalized, and out-patients, including home-isolated ones. Associations between patient characteristics and the development of long COVID symptoms were performed. Moreover, patients were stratified in those reporting at least one long COVID symptom and those reporting two or more.

Finally, for in-patients hospitalized during COVID-19 in our hospital, a longitudinal evaluation of inflammatory markers, including C-reactive protein (CRP), D-dimer, ferritin, interleukin 6 (IL-6), lactated dehydrogenase (LDH) plasma concentration and erythrocyte sedimentation rate (ERS) were performed at two time points: during COVID-19 acute phase (T0) and during evaluation of long COVID symptoms (Tpost).

Statistical analyses

All data are reported as median with interquartile range (IQR). Comparative analyses were performed, specifically the chi-square test or Fisher test to compare frequencies of categorical variables or Student t test, Mann-Whitney test, and Wilcoxon test of quantitative variables. Associations between patient characteristics during SARS-CoV-2 infection and risk of symptoms, alteration of pulmonary functions and immunoglobulin levels were quantified with logistic regression, reporting odds ratios along with their 95% confidence intervals (CI). Results were considered statistically significant if the p value was ≤ 0.05. All analyses were performed with R v4.0.2 and GraphPad Prism v9.2.0.

Ethics

The study was approved by Ethics Committee of Policlinico Umberto I, Sapienza University of Rome (protocol number 298/2020). An informed consent from each patient after a detailed explanation of the study was obtained.

Results

Study population

From May 25th, 2020, to June 12th, 2021, 364 patients (female/male: 152/212; median age 58 [49-86] years) were enrolled. Of these, 67% reported at least one comorbidity.
During COVID-19 acute phase, patients received heparin (53%), corticosteroid (49%), antiviral therapy (36.5%) (Table 1).

Evaluation of long COVID symptoms in stratified population

Overall, 84% of all patients were in-patients (female/male: 116/188; median age 58 [20-86] years). Of these, 33% developed ARDS during COVID-19 acute phase. In 79% of in-patients at least one long COVID symptom was reported, while in 54% two or more symptoms were observed.

Among out-patients (female/male: 36/24; median age 54 [43-62] years), 82% of them reported at least one long COVID symptom, while 67% reported two or more. Long COVID symptoms reported by in- and out-patients during follow up visit are presented in table 1.

Evaluation of inflammatory markers in in-patients

A longitudinal evaluation of inflammatory markers between COVID-19 acute phase (T0) and post-COVID visit (T1) was performed in in-patients. At Tpost, inflammatory markers, white blood cell (WBC) and lymphocyte count were within normal ranges. However, at Tpost, a reduction in C-reactive protein (CRP), D-dimer, erythrocyte sedimentation rate (ERS), ferritin, IL-6, fibrinogen, neutrophil and lymphocyte count and lactate dehydrogenase (LDH) were observed compared to T0 (Table 2, Figure 2).

Long COVID symptoms and clinical features

Overall, during long COVID visit, 290 (80%) patients reported at least one long COVID symptom, while 202 (56%) had two or more. Fatigue was the most frequent symptom.

Patients with two or more symptoms, frequently reported fatigue (52%), dyspnea (52%) and cardiovascular symptoms (40%).

Overall, 277 of all patients performed chest CT during long COVID visit. In 29.9% of cases, no lung involvement was observed. Pattern type 1 with fibrosis and parenchymal bands was presented in 34% of patients, pattern type 2 with GGO was found in 37% of patients. The median CT score was 5/25. In 44.7% of patients, pulmonary function alterations were observed. The 6MWT was performed in 322 patients and desaturation was observed in 9% of them at follow-up (Table 3).

During the long COVID visit, an infectious examination was performed and in sixteen patients bacterial or viral infections were observed after COVID-19. One pulmonary tuberculosis, three herpes simplex reactivations, eleven urinary tract infections (UTI), and one *Clostridium difficile* infection were observed. All patients who reported bacterial or viral infection during long COVID visit were hospitalized during COVID-19 acute phase.

Associations between patient characteristics and long COVID symptoms

Men showed a lower risk of presenting at least one symptom at long COVID visit (OR=0.42, 95% CI 0.23 to 0.73, p=0.003) compared to women, while a higher risk was seen in patients treated with corticosteroid (OR=1.76, 95% CI 1.05 to 3.00, p=0.035) and thromboprophylaxis (OR=1.70, 95% CI 1.02 to 2.88, p=0.045). Moreover, in the multivariable model, a significantly reduced risk of presenting at least one symptom in men was observed (OR=0.34, 95% CI 0.18 to 0.62, p=0.002).

Similarly, the risk of presenting two or more symptoms at long COVID visit was lower in men (OR=0.42, 95% CI 0.25 to 0.29, p≤0.001). In the multivariable model, only male sex was found to significantly reduce the risk of developing two or more symptoms at long COVID visit (OR=0.38, 95% CI 0.20 to 0.68, p=0.001).

Finally, a trend in the risk of developing two or more long COVID symptoms was associated with increased white blood cells (WBC) count (OR=0.908, 95% CI 0.823 to 0.997, p=0.0487) and D-dimer (OR=1.00025, 95% CI 1.00001 to 1.00051, p=0.04798) at T0 (Table 4).

Associations between patient characteristics, Chest CT pattern and pulmonary function

Patients with a higher risk of presenting residual abnormalities at follow-up chest CT were those who have been hospitalized during COVID-19 acute phase (OR=2.17, 95% CI 1.11 to 4.23, p=0.023) and who received hydroxychloroquine treatment (OR=1.92, 95% CI 1.12 to 3.36, p=0.020). Moreover, a higher risk of altered pulmonary function was observed in older patients (OR=1.03, 95% CI 1.01 to 1.04, p=0.001), as well as in patients that had one or more comorbidities (OR=1.39, 95% CI 1.07 to 1.80, p=0.014). More specifically, higher risk of altered pulmonary function was observed in patients who reported having chronic respiratory diseases (OR=2.31, 95% CI 1.24 to 4.40, p=0.009). In the multivariable model, age (OR=1.02, 95%CI 1.01 to 1.04, p=0.012) and respiratory disease (OR=2.12, 95%CI 1.05 to 4.39, p=0.039) were confirmed as risk factors of pulmonary function alterations.

Finally, the risk of developing altered pulmonary function was also observed in patients with high value of CRP and ESR at post-COVID visit. Instead, a trend in the risk of developing altered pulmonary function with increased D-Dimer at T-post and the development of ARDS in the acute phase was observed (Table 5).

Discussion

In this single-center retrospective observational study, the health consequences in adult patients that developed long COVID symptoms were assessed. In line with previously studies, the most frequent long-COVID symptoms were fatigue, dyspnea, cardiovascular symptoms, and neurological signs [1,12–14,30 31,32]. In this manuscript, the prevalence of any long COVID symptom was similar to those reported by Malheiro et al., among both in- and out-patients [33]. The heterogeneity of long COVID symptoms underline that long COVID is a complicated and multidimensional illness [34].

We also assessed lung parenchymal involvement at chest CT. More than two thirds of patients showed CT abnormalities, such as fibrotic alterations or persisting ground grass opacities, among both in- and out-patients. This is in line with recent literature in which long COVID pulmonary alterations were reported with an incidence ranging between 5 and 75% [35–38]. This could support the

model that proinflammatory circuits between infected macrophages and T-cells drive a prolonged viral lung injury, which may be the reason that organizing pneumonia is frequently reported on chest imaging, even weeks later the acute phase [39].

We observed that almost half of the patients showed altered pulmonary functions, although at the 6-minute walk test desaturation in only 9% of individuals was observed. Cytokine storm production and release of tissue injury markers have been extensively described during COVID-19 acute phase [12,40–42] and they have been proposed as the cause of pulmonary function alterations in patients experiencing long COVID symptoms [12,43,44].

After the acute phase of the disease, only few patients referred a viral or bacterial infections. Interestingly, all those patients were hospitalized during COVID-19 and one of those developed tuberculosis. This could be caused by an immune dysregulation due to cytokine storm and lymphopenia [45–47].

Male sex is associated with a lower risk of developing post-acute phase sequelae [48,49]. This finding is consistent with previously published reports in which female sex has been proposed as a risk factor for long COVID development [13]. This could be explained by the different immune responses between men and women, and to the involvement of hormones that might play a role in perpetuating the hyperinflammatory status [48,50]. We also observed a higher risk of developing at least one long COVID symptom in patients that were treated with corticosteroids during COVID-19 acute phase. Corticosteroid treatment might play a role in long COVID development due to its different side effects, such as myopathy [51]. Moreover, corticosteroids are also involved in central nervous system (CNS) symptoms, potentially leading to neuropsychiatric adverse effects, such as anxiety, psychosis, disturbances in sleep and mood fluctuations, with an increase associated risk of sequelae [52,53].

Our results show that age and chronic respiratory diseases are associated with altered pulmonary function in long COVID, as also observed in recent literature [54]. Respiratory disease can affect the lung parenchyma which is more susceptible to long-term damage. Our findings highlight the importance of investigations of persistent radiological abnormalities in long COVID patients. Hydroxychloroquine and hospitalization were found to be associated with the presence of parenchymal alterations on chest CT. As reported by Xi Yin, hospital stay is related to the severity of disease, therefore a more severe disease is likely to be associated with persistent radiological alterations [55]. It is necessary to identify targetable pathways to support the use of therapeutics such as glucocorticoids to mitigate the onset of fibrotic damage earlier.

Lastly, we investigated the involvement of inflammatory markers in long COVID development. The role of biomarkers in long COVID remains unclear [56,57]. Although in several previous publications, high levels of CRP, D-dimer and LDH were observed after COVID-19 acute phase, independently from symptoms severity and lung fibrosis involvement [13,58–61]. In our study, among in-patients, at the long COVID visit a reduction of inflammatory markers such as IL-6, CRP, ferritin, fibrinogen, D-dimer and LDH as well as neutrophil and lymphocyte count was observed. These results are consistent with the study conducted by Sorokina and colleagues, showing a reduction in D-dimer and LDH, as well as in leukocyte count [62]. However, we observed an increasing trend WBC and D-dimer that could be risk factors for the presence of two or more long COVID symptoms, as well as CRP and D-dimer were associated with the development of pulmonary function alterations. Indeed, as reported by Yong and colleagues, D-dimer, CRP, LDH and IL6 might to be increased in long COVID, leading to support their involvement in immunovascular and thrombo-inflammatory events in long COVID pathophysiology [58].

The strengths of this study include its large, unselected study sample recruited from the general population, the multidisciplinary experience and inclusion of patients over the entire spectrum of COVID-19 disease severity (in- and out-patients) and patients with one or more than 2 symptoms.

A further strength is the large number of symptoms included in the analysis, which was based on a recent literature and an extensive consultation with patients and clinicians.

Moreover, to minimize bias, we evaluated chest CT and pulmonary function, allowed us to examine the recovery underling the importance of multidisciplinary approach. Detailed characterization of participants allowed us to adjust for multiple potential confounding factors in multivariable analyses.

Our study has some limitations. This single-center retrospective study included a small sample size of out-patients compared to in-patients. Chest CT and LFT were compared with the standard normal values. Moreover, in our cohort, vaccinated individuals were not included in which long COVID symptoms may evolve differently. Symptoms were self-referred by patient and might not be uniform and accurate. Finally, people younger than 18 years old were not included, reducing generalizability. However, recent reviews report that older age, female sex, severe infection are considered risk factors for long COVID in pediatric survivors, similar to adults [63,64]. Finally, patients living in nursing homes or residences were not included in the study given the unable to participate in the long COVID visit.

On the other hand, our study confirms the lack of correlation between the acute phase of COVID-19 disease and long COVID symptoms reported at follow-up visit as previously reported by Sykes and colleagues [4]. This result suggests that long COVID should be considered a new disease which may involve patients with both mild and severe COVID-19 disease in the acute phase.

Finally, we did not quantify the severity of persistent dyspnea since patients were only asked to report the presence or absence of dyspnea, nor did we have any information on symptoms, pulmonary function, and 6MWT prior to diagnosis with COVID-19.

Future studies should further expand this work to assess the long-term effect of long COVID and vaccine effectiveness in reducing long COVID.

Conclusions

In conclusion, our study highlights the importance of recognizing long COVID in patients with previous mild COVID-19 disease due to the possibility of developing long-term sequelae. To date there are no specific long COVID treatments, however recognizing this syndrome may be crucial to offer patients a more suitable approach. Moreover, a multydisciplinary methodology is essential to implement knowledge for the most appropriate management of COVID-19 patients.

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Characteristics	**In-patients**	**Out-patients**
Patients	304 (84%)	60 (16%)
Female	116 (38%)	36 (60%)
Male	188 (62%)	24 (40%)
Median age (years)(IQR)	58 (20-86)	54 (43-83)
Median days (IQR) of follow-up	85 (46-110)	78 (41-126)
Comorbidities	209 (69%)	36 (60%)
No comorbidities	95 (31%)	24 (40%)
Yes comorbidities	209 (69%)	36 (60%)
0	95 (31%)	24 (40%)
1	87 (29%)	15 (25%)
2 or more	122 (40%)	21 (35%)
Hypertension	132 (43%)	21 (35%)
Cardiovascular disease	51 (17%)	10 (17%)
Respiratory disease	47 (15%)	5 (8%)
Neoplasia	24 (7.9%)	6 (10%)
Diabetes mellitus	35 (12%)	5 (8%)
Chronic renal failure	5 (1.6%)	0 (0%)
Smoke		
never smoker	165 (54%)	29 (48%)
current smoker	22 (7%)	6 (1%)
past smoker	117 (38.5%)	25 (42%)
PAS	121.2	122.4
PAD	74	75.1
ARDS	101 (33%)	-
NON-ARDS	203 (64%)	60 (100%)
Symptoms		
one symptom	241 (79%)	49 (82%)
two or more symptoms	162 (53%)	40 (67%)
fatigue	105 (35%)	24 (40%)
ocular symptoms	12 (4%)	0 (0%)
skin signs	25 (8%)	1 (2%)
dyspnea	103 (34%)	21 (35%)
neurological signs:	40 (13%)	9 (15%)
1) headache	8 (3%)	2 (3%)
2) loss of memory and concentration	14 (5%)	5 (8%)
3) paresthesia	13 (4%)	2 (3%)

	sleep and mood disorders	63 (21%)	10 (17%)
	cardiovascular symptoms	77 (25%)	20 (33%)
	dysgeusia	18 (6%)	11 (18%)
	anosmia	19 (6%)	14 (23%)
	GI disorders	17 (6%)	2 (3%)
	arthralgia	28 (9%)	10 (17%)
	hair loss	23 (8%)	1 (2%)
	cough	14 (5%)	5 (8%)
Therapies			
	hydroxychloroquine	144 (47%)	3 (5%)
	anti-Il-6	79 (26%)	-
	corticosteroids	149 (49%)	31 (52%)
	heparin	173 (57%)	20 (33%)
	antiviral therapy	124 (40.8%)	9 (15%)
Chest CT		234 (77%)	43 (71.7%)
PF		277 (91.1%)	59 (98.3%)
6-MWT		271 (89.1%)	56 (93.3%)

Table 1. Clinical and demographic characteristics of study population
N: Number; IQR: Interquartile Range; GI: gastrointestinal; Chest CT: Chest Computed Tomography;PF:Pulmonary Function; 6-MW: 6-Minute Walking Test. Data are presented as median with interquartile range. Proportions are expressed both as numbers and percentages.

	T0	**Tpost**	***p* value**
patients	304	304	
female/male	116/188	116/188	
median age, years	58 [50-68]	58 [50-68]	
inflammatory markers			
CRP (mg/dL)	2.20 [0.51-5.65]	0.13 [0.07-0.27]	**<0.0001**
D-dimer (μg/mL)	683 [401-1258]	341 [231-578.8]	**<0.0001**
ESR (mm/h)	38 [21-53]	13 [7-23]	**<0.0001**
ferritin (ng/mL)	451 [226.8-901.5]	107.5 [57.25-227.0]	**<0.0001**
fibrinogen (g/L)	306 [4.99-541.5]	3.06 [2.64-3.57]	**<0.0001**
IL-6 (pg/ml)	17 [6.10-43.67]	3.19 [1.78-6.81]	**<0.0001**
LDH (U/L)	237 [194.5-311.0]	179 [162-203]	**<0.0001**
blood cell counts			
WBC ($x10^9$/L)	5.55 [4.07-7.21]	5.81 [4.95-7.05]	0.0733
N ($x10^9$/L)	3.58 [2.46-5.24]	3.24 [2.56-4.01]	**0.0003**
L ($x10^9$/L)	1.14 [0.78-1.59]	1.87 [1.50-2.29]	**<0.0001**
PLT ($x10^9$/L)	221 [163-299.5]	220 [188-266]	0.0932

Table 2. Evaluation of inflammatory markers and blood cell counts at baseline and at follow up. Data are presented as median and interquartile ranges. Statistical analysis was performed using the nonparametric Wilcoxon test. T0: acute COVID-19 phase; Tpost: follow up during long COVID evaluation. CRP: C reactive protein; ESR: erythrocyte sedimentation rate; IL-6: Interleukin 6; LDH: lactate dehydrogenase; WBC: white blood cell; N: neutrophils; L: leukocytes; PLT: platelets

	All patients (n=364)	=1 symptoms (n=290)	≥2 symptoms (n=202)
Female	152 (42%)	133 (46%)	105 (51%)
Male	212 (58%)	158 (54%)	97 (49%)
Age	57 (18-86)	57 (18-86)	57 (49-66)
Median days from discharge	82 (46-112)	84 (52-112)	86 (56-110)
Smoke			
Current smoker	27 (7%)	23 (8%)	16 (8%)
Past smoker	141 (39%)	104 (36%)	67 (33%)
Never	196 (54%)	163 (56%)	124 (61%)
Comorbidities		195 (57%)	139 (69%)
none	119 (33%)	96 (33%)	63 (31%)
at least one	102 (28%)	81 (28%)	56 (28%)
two or more	143 (39%)	114 (39%)	83 (41%)
hypertension	153 (42%)	122 (42%)	88 (44%)
cardiovascular disease	61 (17%)	46 (16%)	34 (17%)
respiratory disease	52 (14%)	43 (15%)	32 (16%)
neoplasia	30 (8%)	24 (8%)	18 (9%)
chronic renal failure	5 (1%)	3 (1%)	3 (2%)
diabetes mellitus	40 (11%)	31 (11%)	25 (12%)
Treatment			
hydroxychloroquine	147 (40%)	120 (41%)	85 (42%)
anti-IL-6	79 (22%)	66 (23%)	48 (24%)
corticosteroids	180 (49%)	152 (52%)	105 (52%)
heparin	193 (53%)	162 (56%)	109 (54%)
antiviral therapy	133 (37%)	110 (38%)	76 (38%)
Hospitalization		241 (83%)	162 (80%)
ARDS	100 (27%)	82 (28%)	50 (25%)
non-ARDS	264 (73%)	208 (72%)	151 (75%)
Symptoms			
fatigue	129 (36%)	129 (44%)	106 (52%)
ocular symptoms	12 (3%)	12 (4%)	11 (5%)
skin signs	26 (7%)	26 (9%)	25 (12%)
dyspnea	124 (34%)	124 (43%)	105 (52%)
neurological signs:	49 (13%)	49 (17%)	48 (24%)
headache	10 (3%)	10 (3%)	10 (5%)
loss of memory and concentration	19 (5%)	19 (7%)	19 (9%)
paresthesia	15 (4%)	15 (5%)	15 (7%)
sleep and mood disorders	73 (20%)	73 (25%)	63 (31%)
cardiovascular symptoms	97 (27%)	97 (33%)	82 (41%)
dysgeusia	29 (8%)	29 (10%)	26 (13%)
anosmia	33 (9%)	33 (11%)	32 (16%)
GI disorders	19 (5%)	19 (7%)	17 (8%)
arthralgia	38 (10%)	38 (13%)	33 (16%)
hair loss	24 (7%)	24 (8%)	21 (10%)
cough	19 (5%)	19 (7%)	14 (7%)
HRCT	277 (76%)		
median CT Score	5 (0-8)		
pattern 1	95 (34%)		
pattern 2	102 (37%)		
no lung involvement	83 (29.9)		
Pulmonary function	333 (91.5%)		
alterations	149 (44.7%)		
normal	184 (55.3%)		
6MWT	322 (88.5%)		
desaturation	29 (9%)		

Table 3. Clinical features and long COVID symptoms in study population
n: number; IQR: Interquartile range; GI: gastrointestinal; HRCT: high resolution chest tomography; 6MWT: 6-minute walking test; anti-S antibody titers: anti-Spike antibody titers. Data are presented as median with interquartile ranges. Proportions are expressed as both numbers and percentages.

Explanatory	Univariate At least one symptom	Univariate Two symptoms or more	Multivariate At least one symptom	Multivariate two symptoms or more
Male sex	0.42 (0.23-0.73, **p=0.003**)	0.38 (0.25-0.59, **p<0.001**)	0.38 (0.20-0.68, **p=0.002**)	0.39 (0.21-0.68, **p=0.001**)
Age	0.99 (0.97-1.01, p=0.295)	0.99 (0.98-1.01, p=0.448)	0.99 (0.97-1.01, p=0.235)	1.00 (0.98-1.01, p=0.620)
Comorbidity	0.93 (0.53-1.61, p=0.809)	1.13 (0.73-1.77, p=0.576)		
Hypertension	0.98 (0.58-1.65, p=0.809	1.15 (0.75-1.75, p=0.527)		
Cardiovascular disease	0.73 (0.39-1.43; p=0.340)	0.99 (0.57-1.73, p=0.970)		
Respiratory disease	1.23 (0.59-2.82; p= 0.594)	1.31 (0.72-2.42, p=0.382)		
Neoplasia	1.00 (0.42-2.80, p=0.994)	1.32 (0.61-2.96, p=0.490)		
Diabetes mellitus	0.85 (0.40-1.97, p=0.683)	1.36 (0.70-2.72, p=0.378)		
Chronic renal failure	0.37 (0.06-2.85, p=0.281)	1.18 (0.19-9.07, p=0.855)		
Hospitalization	0.77 (0.35-1.54, p=0.474)	0.58 (0.32-1.03, p=0.069)	1.05 (0.43-2.45, p=0.905)	0.66 (0.16-2.28, p=0.523)
Therapies				
Corticosteroid	1.76 (1.05-3.00, **p=0.035**)	1.22 (0.80-1.85, p=0.351)	1.52 (0.78-3.01, p=0.226)	
Heparin	1.70 (1.02-2.88, **p=0.045**)	1.10 (0.73-1.67, p=0.652)	1.41 (0.74-2.71, p=0.294)	
Hydroxychloroquine	1.20 (0.71-2.05, p=0.508)	1.14 (0.75-1.75, p=0.536)		
Anti-IL-6	1.35 (0.72-2.71, p=0.368)	1.25 (0.75-2.10, p=0.388)		
Blood test at acute phase				
WBC	0.89 (0.76-1.04, p=0.137)	0.908 (0.823-0.997, **p=0.0487**)		
N	1.01 (0.93-1.13, p=0.844)	0.99 (0.91-1.07, p=0.810)		
L	1.02 (0.72-1.51, p=0.928)	1.00 (0.73-1.36, p=0.981)		
PLT	1.00 (1.00-1.00, p=0.977)	1.00 (1.00-1.00, p=0.599)		
IL-6	1.01 (0.99-1.03, p=0.312)	1.01 (1.00-1.03, p=0.078)		
CRP	1.01 (0.99-1.05, p=0.549)	0.98 (0.94-1.00, p=0.138)		
D-dimer	1.00 (1.00-1.00, p=0.753)	1.00025 (1.00001-1.00051, **p=0.04798**)		
LDH	1.00 (1.00-1.00, p=0.558)	1.00 (1.00-1.00, p=0.911)		
Ferritin	1.00 (1.00-1.00, p=0.807)	1.00 (1.00-1.00, p=0.087)		
ESR	1.01 (0.99-1.02, p=0.385)	1.00 (0.99-1.02, p=0.524)		
Fibrinogen	1.00 (1.00-1.00, p=0.675)	1.00 (1.00-1.00, p=0.513)		

Table 4. Association between patients' characteristics and long COVID symptoms
T0: COVID-19 acute phase; WBC: white blood cell; PLT: platelets; CRP: C-reactive protein. LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; Data are reported as odds ratios along with their 95% confidence intervals (95%CI).

explanatory	Univariate altered chest CT	Multivariate altered chest CT	Univariate altered pulmonary function	Multivariate altered pulmonary function
Male sex	1.22 (0.72-2.05, p=0.456)	1.15 (0.67-1.96, p=0.617)	0.90 (0.58-1.39, p=0.620)	0.79 (0.49-1.26, p=0.321)
Age	1.01 (0.99-1.03, p=0.204)	1.01 (0.99-1.03, p=0.328)	1.03 (1.01-1.04, p=0.001)	1.02 (1.01-1.04, **p=0.012**)
Number of Comorbidities	0.91 (0.67-1.23, p=0.546)		1.39 (1.07-1.80, p=0.014)	1.01 (0.67-1.50, p=0.970)
Hypertension	0.99 (0.59-1.67, p=0.970)		1.53 (0.99-2.38, p=0.056)	1.07 (0.56-2.05, p=0.839)
Cardiovascular disease	1.28 (0.67-2.57, p=0.475)		1.33 (0.75-2.39, p=0.329)	
Respiratory disease	1.07 (0.52-2.35, p=0.861)		2.31 (1.24-4.40, p=0.009)	2.12 (1.05-4.39, **p=0.039**)
Neoplasia	0.82 (0.33-2.24, p=0.680)		1.71 (0.79-3.82, p=0.178)	
Diabetes mellitus	1.56 (0.68-4.04, p=0.324)		1.26 (0.64-2.49, p=0.503)	
Hospitalization	2.17 (1.11-4.23, p=0.023)	1.67 (0.80-3.48, p=0.168)	1.19 (0.67-2.13, p=0.552)	
ARDS-NON-ARDS	1.26 (0.71-2.20, p=0.418)		0.6136 (0.3753-0.9987, **p=0.04991**)	
Hydroxychloroquine	1.92 (1.12-3.36, **p=0.020**)	1.63 (0.73-3.57, p=0.227)	0.75 (0.48-1.16, p=0.198)	
Corticosteroid	1.07 (0.64-1.79, p=0.810)		1.47 (0.95-2.27, p=0.083)	
Heparin	0.88 (0.52-1.47, p=0.623)		1.43 (0.93-2.22, p=0.103)	
Blood test Tpost				
WBC	0.98 (0.83-1.15, p=0.779)		1.09 (0.95-1.25, p=0.216)	
N	1.00 (0.79-1.27, p=0.993)		1.16 (0.95-1.42, p=0.151)	
L	0.92 (0.65-1.34, p=0.653)		1.00 (0.73-1.37, p=0.994)	
PLTs	1.00 (0.99-1.00, p=0.403)		1.00 (1.00-1.01, p=0.259)	
IL-6	0.99 (0.97-1.01, p=0.245)		1.01 (1.00-1.03, p=0.134)	
CRP	1.33 (0.79-2.85, p=0.376)		2.09 (1.23-4.00, **p=0.015**)	
D-Dimer	1.00 (1.00-1.00, p=0.294)		1.00047 (1.00003-1.00096, p=0.045731)	
LDH	1.00 (0.99-1.01, p=0.957)		1.00 (1.00-1.01, p=0.218)	
Ferritin	1.00 (1.00-1.00, p=0.685)		1.00 (1.00-1.00, p=0.128)	
ESR	1.00 (0.99-1.02, p=0.740)		1.03 (1.02-1.05, **p<0.001**)	
Fibrinogen	1.11 (0.97-1.62, p=0.585)		0.99 (NA-1.00, p=0.402)	

Table 5. Associations between patients characteristics, TC pattern and pulmonary function
Tpost: post-acute phase of CODIV-19; WBC: white blood cell; PLTs: platelets; CRP: C-reactive protein; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate;. Data are reported as odds ratios along with their 95% confidence intervals (95%CI).

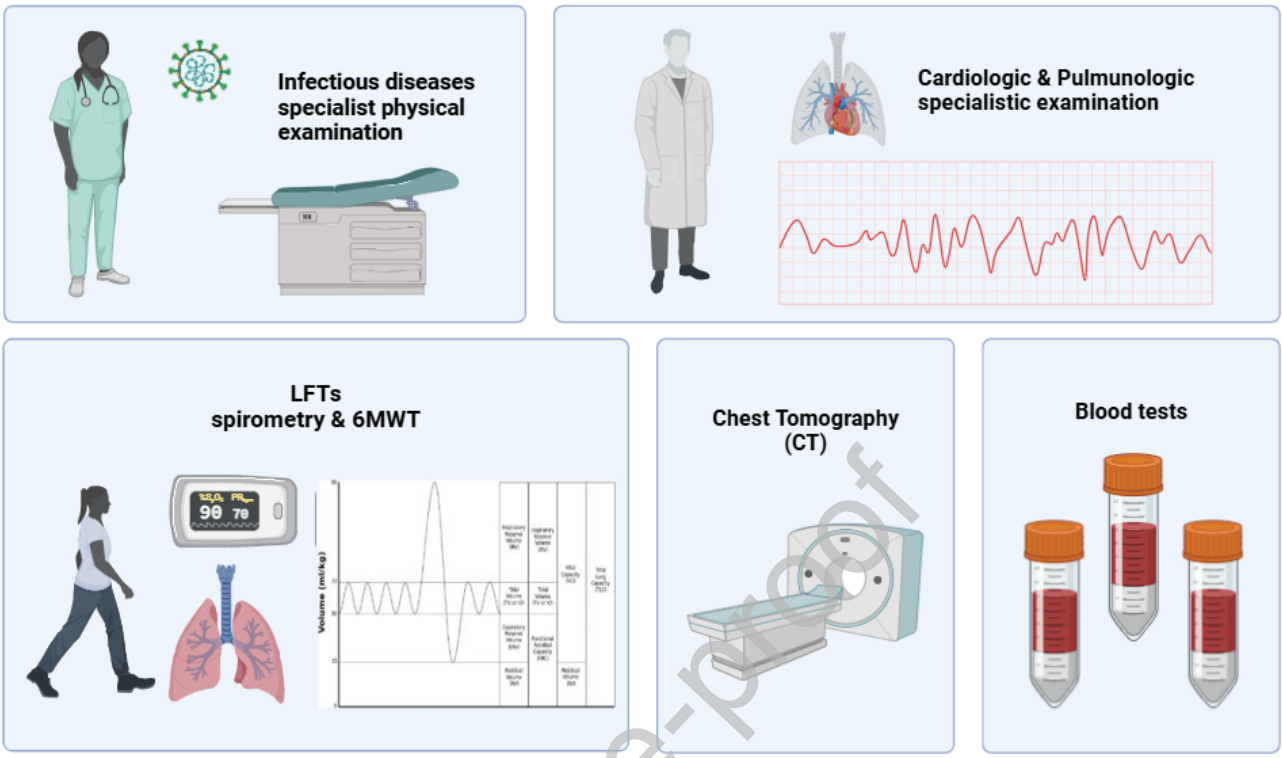

Figure 1. Long COVID clinic organization. LFT: Lung Function Testing; 6MWT: 6 Minute Walking Test; Chest CT: Computed Tomography.

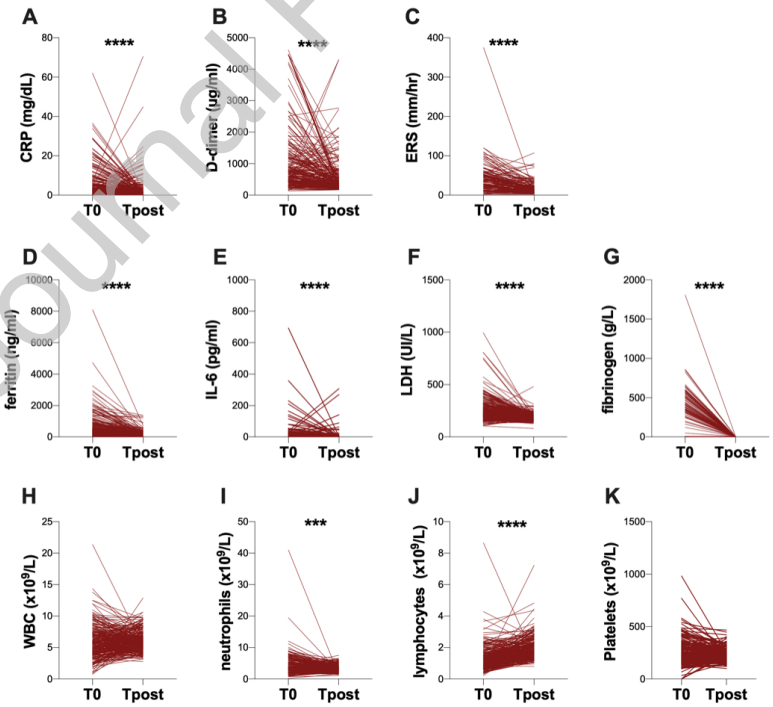

Figure 2. Longitudinal evaluation of inflammatory markers and blood cell count between baseline and follow up in in-patients.

Longitudinal evaluation of inflammatory markers(CRP (A), D-Dimer (B), ESR (C), ferritin (D), IL-6 (E), LDH (F), fibrinogen (G) and blood cell count (WBC(H), neutrophils (I), lymphocytes (J), platelets (K)) between baseline (T0) and follow up (Tpost). Statistical analysis was performed using the nonparametric Wilcoxon test. *p < 0.05; **p < 0.01;

***p < 0.001; ****p < 0.0001. CRP: C reactive protein; ESR: erythrocyte sedimentation rate; IL-6: Interleukin 6; LDH: lactate dehydrogenase; WBC: white blood cell; N: neutrophils; L: leukocytes; PLT: platelets