SEX-RELATED DIFFERENCES IN LONG COVID-19 SYNDROME

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Running title: sex differences in Long-COVID

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Abstract

Background: Sex-differences have been demonstrated in the acute phase of COVID-19 infection; females (F) were found to be less prone to develop a severe disease than males (M), but few studies have assessed sex-differences in Long-Covid-19 syndrome.

Aim and Results: The aim of this prospective/retrospective study was to characterize the long- term consequences of this infection from a sex-perspective. For this purpose, we enrolled 223 patients (89 F and 134 M) who experienced a SARS -CoV-2 infection. In the acute phase of the illness, females reported more frequently than males: weakness, dysgeusia, anosmia, thoracic pain, palpitations, diarrhea, and myalgia without significant differences in breathlessness, cough, and sleep disturbance. After a mean follow-up time of 5 months after the acute phase, females were significantly more likely than males to report weakness, thoracic pain, palpitations, and sleep disturbance but not myalgia and cough.

At the multivariate logistic regression, women were statistically significantly likely to experience persistent symptoms such as dyspnoea, fatigue, chest pain, and palpitations. On the contrary, myalgia, cough and sleep disturbance were not influenced by sex.

Conclusion: We demonstrated that females were more symptomatic than males not only in the acute phase but also at follow-up. Sex was found to be an important determinant of Long-COVID syndrome because it is a significant predictor of persistent symptoms in females, such as dyspnoea, fatigue, chest pain, and palpitations.

Our results suggest the need for long-term follow-up of these patients from a sex-perspective in order to implement early preventive and personalized therapeutic strategies.

Key Words: sex, gender, SARS CoV-2, COVID 19, Long-COVID-19 syndrome, long-term outcome

Introduction

T*he Pandemic has finally opened our eyes to the fact that health is not driven just by biology, but by the social environment in which we all find ourselves, and gender is a major part of that*." This affirmation is from Professor Sarah Hawkes, Co-Director of Global Health 50 (GH5050), underling the role of Gender Medicine.[1]

Indeed, during the COVID-19 pandemic, significant sex and gender differences were observed in terms of susceptibility, symptoms, severity, and mortality. More males died from this infection, needed intensive care, showed higher pulmonary involvement, and were assessed as having chest High Resolution computed tomography (HRCT) score, and a higher increase of some laboratory parameters, such as C-reactive protein (CRP), D-Dimer, and transaminases. However, in the acute phase, females reported a greater variety of symptoms, specifically, diarrhea, disturbances of smell, taste, and headaches.[2-5]

Today, there is a growing body of evidence that a great number of patients with a history of SARS CoV-2 infection complain of a persistent symptomatology, with higher percentages in the critical patients versus those with the mild form of the illness. [6-10] Carfi et al. found, in a mean follow-up of 60 days, that 87.4% of patients who had recovered from COVID-19 reported the persistence of at least 1 symptom, particularly fatigue and dyspnoea, with only 12.6% reporting to be asymptomatic.[7] Nevertheless, few studies have described the sex-and gender-disaggregated data on the sequelae of the infection that have the potential to be so useful for identifying the specific factors involved in the pathophysiology of Long- COVID-19 syndrome and for implementing early preventive and personalized therapeutic strategies.[11]

In the UK, Sigfrid L. et al. demonstrated that, despite higher mortality in males in the acute phase, females seem to be at higher risk for developing long-term COVID-19.[12]

The aim of this prospective/retrospective study is to characterize, from a sex-and gender-perspective, the long- term consequences of COVID-19 infection. We also analyzed the predictors of post-COVID-19 syndrome in male and female groups, regarding the acute care clinical setting as well as risk factors, comorbidities, and lifestyle behaviors in order to create a personalized medical treatment plan.

For this purpose, we enrolled a large cohort of patients who experienced SARS -CoV-2 infection and who underwent a multidisciplinary evaluation after SARS CoV-2 infection at the University-Hospital of Parma.

Methods

Study Design and Participants

This is a monocentric retrospective-prospective study that includes 223 consecutive patients who had been discharged from the ward or from the outpatient clinic after a diagnosis of COVID-19 during the first three waves of the pandemic, and, who were subsequently referred for a follow-up visit at the University-Hospital of Parma between May 2020 and March 2021.

The study protocol was approved by the Local ethics committee AVEN (RESPCOV-2, *Protocol n.* 681/2020/SPER/AOUPR). Written informed consent was obtained from all participants.

Exclusion criteria were two-fold: a history of significant heart or/and respiratory disease and an unwillingness to participate or to provide informed consent. Three patients were

excluded, one was affected by Marfan syndrome with severe mitral insufficiency, and two were affected by generalized sarcoidosis.

At the time of follow-up, the presence of symptoms, particularly dyspnoea, asthenia, heartbeat, chest pain, cough, anosmia, dysgeusia, diarrhea, myalgia, weight loss, and alterations in the sleep-wake rhythm, were recorded. Medical histories, comorbidities such as a history of hypertension, cardiovascular diseases (CVDs), chronic respiratory diseases (CRDs), and diabetes, and pharmacological therapy before COVID-19 infection were also considered.

Data regarding clinical characteristics (age, sex, and anthropometric parameters), educational level (<11 years, between 11-13 years, >13 years), marital status (single/separate/divorced, married/cohabiting, widowed), and work/profession were collected.

Detailed information on lifestyle, high risk behaviors, including smoking and alcohol consumption, and level of physical activity (PA), considering, when appropriate, type, intensity and duration of PA, in the last year before COVID-19 infection, were also recorded.

Retrospective data about symptoms in the acute phase, hospitalization, i.e., Intensive care Unit stays, days of hospitalization, severity of lung involvement - as defined by a score of HRCT (128-slice scanner, SOMATOM Definition Edge, Siemens Healthineers, Erlangen, Germany), respiratory gas exchange, and oxygen supplementation during hospitalization, cardiovascular complications, pharmacological treatment and outcomes, were also collected. Laboratory data at hospital admission, when available, were collected, including D-dimer and C-reactive protein (CRP).

Statistical analysis

Quantitative variables are reported as means ± SD or median (IQ range) depending on the normality (K-S test) and were compared using T Test or Mann-Whitney U test. Qualitative variables are reported as absolute and % prevalence and compared using the χ^2 test or Fisher's exact test.

McNemar's test was used to evaluate the persistence in each symptom reported in male and female groups from baseline to follow-up.

A multivariate logistic regression analysis was performed to explore variables associated with post-COVID-19 syndrome. The variables were identified by univariate logistic regression analysis, including those that correlated significantly with the symptoms at follow-up. The inclusion criterium was a p value <0.1 at the univariate analysis. In this analysis we considered sex, age, BMI, data of acute care clinical setting, comorbidities, lifestyle behaviors, and pharmacological treatment prior to SARS CoV-2 infection. Multicollinearity was always excluded by checking univariate Pearson's correlation coefficients

A 2-tailed p value<0.05 was considered as statistically significant. SPSS v 26 statistical package was used for all analyses (IBM, Amork, NY).

Results

Clinical characteristics

Table 1 shows the main characteristics of the study population enrolled: 89 (40%) were female (F) and 134 (60%) male (M) (mean age was 59$\pm$13 years). The mean body mass index (BMI) was higher than normal in both groups (M:28$\pm$4; F:28$\pm$7 Kg/m^2) with 30% (66/223) of the obese sample having BMI value >30 Kg/m². Systolic blood pressure

(SBP) was significantly higher and HR lower in M as compared to F (Table 1). The prevalence of comorbidities, hypertension, coronary artery diseases, diabetes mellitus, and chronic respiratory diseases, were more frequent in M as opposed to F, without significant differences. No difference in smoking status was found in the two groups, but, in the M group, former smokers prevailed (55 vs 26%) (Table 1).

Twenty-three percent of the participants were on β-blockers, 17% on ACE-inhibitors, 14% on Angiotensin II Receptor Blockers (ARB), and 18% on antiplatelet therapy in the period prior to infection. No differences were found in current therapy, when patients were categorized according to sex.

Lifestyle of the two groups was analyzed in terms of physical activity, i.e., a sedentary or physically active life, and we did not found significant differences between M and F (Table 1).

Similarly, educational level and marital status were similar in the two groups but a significant difference was observed in profession/work between M and F (Table 1).

Acute COVID-19 characteristics

The distribution of HRCT visual score (available in 170 patients, with 53 missing data) is depicted in Figure 1 and shows a slight increase in M compared to F (p=0.066).

Data regarding the severity and the course of the acute disease is shown in Table 2. Seventy-two (n=162) percent of the population enrolled had been hospitalized at the University-Hospital of Parma with higher percentages among M than among F (79% vs 63% F, p=0.017) and without significant differences for length of stay (M:25$\pm$26 vs F 23$\pm$17 days) (Table 2 and Figure 1). Fifty-seven patients (28%) were cared for at home

(M=21%; F=37%). Seventeen percent of hospitalized patients needed to be transferred to the Intensive Care Unit (ICU), 18% of males and 16% of females (p=ns), respectively, while the remaining 82% of hospitalized patients continued their treatment in a non-intensive Unit. More males received oxygen therapy (total population 66%; F=53% vs M= 75%; p=0.001): Oxygen with mask was required in a greater number of males than females (48 M vs 31% F, P=0.013); while non-invasive ventilation (NIV) with a C-PAP helmet and invasive mechanical ventilation were similar in the two groups. CV complications did not differ in the two groups (Table 2).

Regarding laboratory data, CRP and D-dimer were higher in males than in females (Figure 1).

Taken together, these data suggest a greater severity of the disease in males.

More males than females were treated with antivirals (47 vs 34%, respectively, p=0.077), while more females received systemic corticosteroids (55 vs 42%, respectively, p=0.07). There were no substantial sex-based differences in the antibiotics, Hydroxycloroquine, Colchicine, and low molecular weight Heparin in the prophylactic dose or in the therapeutic dose (Table 3).

Symptoms during the infection: retrospective data

The symptoms in the acute phase of the disease were carefully investigated and stratified by sex. The most common reported symptom was fever (93%) followed by dyspnoea, with 82 % of people experiencing increased breathlessness. Other common symptoms included cough (65%), weigh loss (75%), dysgeusia (57%), anosmia (47%),

fatigue (45%), chest pain (36%), diarrhea (28%), palpitations (27%), myalgia (26%), and alterations in the sleep-wake rhythm (18%).

There were no significant differences between males and females in dyspnoea (83 vs 80%) and cough (62 vs 69%), or in sleep disturbance (15 vs 23%) (Figure 2, on the top). Fatigue, chest pain, dysgeusia, anosmia, palpitations, diarrhea and myalgia were reported more frequently by females (53 vs 38%, p=0.023; 47 vs 29%, p=0.006; 65 vs 51%, p= 0.034; 59 vs 40%, p=0.002; 36 vs 22%, p=0.013; 39 vs22; p=0.005; 34 vs 21%, p=0.022, respectively). A greater percentage of males than females reported weight loss (79 vs 68%; p=0.048) (Figure 2, on the top).

Symptoms at follow-up: prospective data

The majority of patients were still symptomatic with at least one symptom after a median follow-up of 23 weeks (160±80 days; 37-491 days; 5 months). The symptoms during the follow-up period have been compared to those in the acute phase: dyspnea, albeit with reduced percentages (69 vs 82%), was the most frequent symptom, followed by asthenia, which, instead, was reported to a greater extent at follow-up (53 vs 45%), and palpitations (32 vs 27%) as well as alterations in the sleep-wake rhythm, which were markedly increased (46 vs 18%). Chest pain persisted with lower percentages (29 vs 36%), while a marked decrease in cough (10 vs 65%) was also reported.

Regarding sex-differences, females were more symptomatic than males at follow-up (Figure 2, on the bottom): females were significantly more likely than males to report dyspnea (79 vs 63%, p=0.008), weakness (75 vs 39%, p= 0.000), chest pain (43 vs 19%, p= 0.000), palpitations (46 vs 22%, p= 0.000), and sleep disturbance (60 vs

37%, p=0.001) but not myalgia and cough; symptom almost disappeared at follow-up in both groups.

By means of McNemar test, different spectrums of sequelae of Long COVID-19 infection were found among males than females: Males improved significantly in dyspnoea ($p<0.001$) and thoracic pain ($p=0.018$), without changes in fatigue and palpitations. By contrast, females did not improve in dyspnea and thoracic pain, and worsened in fatigue ($p=0.000$) and palpitations ($p=0.047$). Both groups improved with regards to cough ($p<0.001$ for both) and myalgia (M: $p=0.068$; F: $p=0.012$) and worsened in terms of sleep disturbance ($p<0.000$ for both) (Figure 3).

Determinants of long COVID

The determinants of Long-COVID symptoms, such as dyspnea, fatigue, chest pain, palpitations, myalgia, and sleep disturbance, were analyzed by multivariate regression analysis.

Sex was a powerful determinant of the persistence of dyspnea, chest pain, fatigue, and palpitations but did not influence sleep disturbance and myalgia. An inverse correlation was found between age and certain symptoms, including fatigue, palpitations, and chest pain (Table 4).

Some symptoms in the acute phase, such as dyspnea, chest pain, palpitations, myalgia, and sleep disturbance, were predictors of the persistence of the same symptom reported during SARS CoV-2 infection (Table 4).

Furthermore, dyspnea at follow-up was also correlated with BMI, CRDs, and weight loss during the infection was a predictor of fatigue (Table 4). Cough was found to be inversely correlated with hospitalization.

Lastly, sleep disturbance was found to have a significant correlation to certain variables, including the level of physical activity prior to infection (i.e., sedentary, physically active, or high levels of physical activity), CPAP, and headache (Table 4).

Discussion

The present study demonstrates that Long COVID syndrome is different among females and males, thus underlining the need to study this disease from a sex perspective in order to implement personalized and targeted medical treatments. To this end, studying the different clinical settings of post-COVID infection in both females and males makes it possible to elucidate the pathophysiology and the risk factors, as well as the relationships between the persistence of symptoms and acute clinical care in terms of their potential therapeutic implications.

Long COVID syndrome is defined as a persistent symptomatology extending beyond 12 weeks after the initial symptoms of the acute infection.[13] The most frequent symptoms reported at follow-up were fatigue, dyspnoea, chest pain, palpitations, and sleep disturbance. [6-12] Many studies on this topic have been published thus far, but there are few with sex and gender disaggregated data.[11]

Our prospective-retrospective study, which began in May 2020, evaluated 223 consecutive patients (M 60%, F 40%) who entered the post-COVID-19 multidisciplinary re-evaluation process, during the first three distinct waves of the virus.

Among these patients, 72% of them had been hospitalized, with 17% requiring transfer to ICU for mechanical ventilation.

In the retrospective analysis, the most frequent symptoms, besides fever, were dyspnoea, cough, and asthenia, followed by chest pain, palpitations, dysgeusia, and anosmia. Diarrhea, nausea/vomiting, myalgia, and sleep disturbances were less frequent. Moreover, 75% of patients reported marked weight loss.

By comparing male and female patients, we demonstrated that, with the exception of dyspnoea and cough, which were equally present in both sexes, the other symptoms were significantly more frequent in females than in males; females complained more frequently of diarrhea, anosmia, chest pain, dysgeusia, asthenia, palpitations, and myalgia. Lastly, there were sleep disturbances, which although close to the threshold of significance, turned out to be more frequent in females, while weight loss was more often reported by males.

These results are in agreement with the literature which showed that the females have more intense symptoms in the acute phase, although the clinical course and prognosis are more severe in males.[11,14] Similarly, in our study, males had a higher HRCT score, a greater increase in phlogosis indices and D-dimer, and a greater need for oxygen support, although no significant differences were observed with regard to CPAP and the need for mechanical ventilation. Pharmacological treatment did not differ substantially in the two groups, which mainly consisted of antibiotics, hydroxychloroquine, and a prophylactic dose of heparin; males were treated with antivirals slightly more frequently than females, while females received more steroid therapy than males. A low percentage of patients in both groups received heparin at therapeutic doses.

In the prospective part of the study, given an average follow-up of 5 months from the infection, we demonstrated that Long-COVID syndrome shows great differences between the two sexes.

Ninety-one percent of our patients evaluated at follow-up continued to experience COVID-19 symptoms, with breathlessness being the most common symptom of Long COVID (69%), immediately followed by fatigue (53%).

Our data are in line with the literature which shows that such symptoms are the most representative ones in post-COVID infection. Carfi A. et al.[7] report persistent symptoms in 143 patients (mean age 56±14) evaluated after hospitalization due to COVID-19 and note that 87% of patients had at least 1 symptom, particularly fatigue and dyspnoea (53 and 43%, respectively), with only 13% reported as being completely free of any COVID-related symptom. Halphin et al.,[6] evaluated 100 patients by means of a telephone survey, 68 cared for in hospital wards and 32 admitted to an Intensive Care Unit, and confirmed that fatigue was the prevalent symptom (72%), followed by dyspnoea (65%).

On the other hand, Sudre C. et al.,[15] in a prospective observational cohort study on COVID-19 symptoms in a subset of 4182 users of the COVID symptoms Study app (mean age of the patients 42 years), found that only 13.3% reported symptoms lasting ≥ 28 days, 4.5% for ≥8 weeks and 2.3% for ≥12 weeks. Similarly, in a survey of 451 non-hospitalized patients at the 4-month follow-up, both fatigue and dyspnea were complained of, with a prevalence of 16%.[10]

It should be noted that, currently, the medical literature on the topic of post-acute COVID-19 includes studies which enrolled patients of different ages, suffering from a wide spectrum of acute COVID-19: from mild infection to critical illness; hospitalised

or cared for at home; and assessed by different methodologies, i.e., medical assessment with physical examination,[7] online surveys [9] or by means of a specialised telephone screening tool. [6]

Therefore, the different results in Long-COVID syndrome can be explained by the heterogeneity of the included patients. However, not all studies report retrospective data on the course of the disease, pharmacological treatment implemented in the acute phase of the infection, laboratory markers such as CRP and D-dimer, pulmonary damage assessed as HRCT score, and comorbidities.[6,7] In addition, these studies did not analyse sex- and gender-disaggregated data on Long COVID-19 syndrome.[6-10]

We demonstrated that Long COVID may significantly differ among males and females: Females were more symptomatic than males (97% vs 84%), with a great percentage reporting persistent COVID-19 symptoms, such as dyspnoea, fatigue, thoracic pain, palpitations, and sleep disturbances. In contrast, cough and myalgia were common in both groups.

By evaluating the changes in symptoms with respect to the acute phase, profound differences were found between females and males. Dyspnoea, the most common persistent symptom, improved significantly in males, while it persisted in females without significant change. The second most frequently reported symptom was fatigue. At the time of follow-up, which occurred after approximately 5 months, about half of our patients complained of intense fatigue and difficulty in performing even the most common activities of daily living. In males, asthenia persisted unchanged at follow-up as compared to the acute phase, but it worsened significantly in females. The same differences reported for asthenia with regards to male and female patients were reported for palpitations. Chest pain and dyspnoea improved in males but persisted

unchanged in females. Both groups improved significantly for cough and myalgia, while they worsened as far as sleep disturbances were concerned.

Multivariate logistic regression was performed to analyse the predictors of long lasting COVID-19 symptoms. We found that females were statistically significantly likely to experience persistent symptoms such as dyspnoea, fatigue, chest pain, and palpitations. In contrast, myalgia, cough and sleep disturbance were not influenced by sex. Thus, sex plays a role in the Long COVID-19 syndrome, confirming previous studies which have shown that being a female was significantly associated with an increased risk of developing persistent symptoms.[15,16]

Many studies have provided ample justification for the differences between males and females in the acute phase of COVID-19 infection, some related to sex-linked biological factors (sex hormones and sex chromosomes) and some related to gender (such as as high risk behaviours including smoking and alcohol consumption, high-risk jobs, and comorbidities, this last one being more frequent in males).[17-19] However, up until now, there was no clear evidence explaining why females were more likely to experience long-lasting COVID-19 symptoms.

Some hypotheses can be proposed: The first one is that the female sex has a more marked perception of pain.[20] The literature suggests that females report somatic symptoms more frequently than males in both the medical and community settings, attributed to physiological factors: sex hormone profiles and differences in the functioning of the innate and adaptive immune systems may be related to the experience of pain.[20,21]

Secondly, gender-related social factors may attribute the *strong* sex stereotype to masculinity, whereby men are thought to have a higher pain threshold and tolerance, while women are thought to have a lower threshold.

Thirdly, sex-related differences in symptom manifestations have been demonstrated in some respiratory and cardiovascular diseases. In asthma, females were more likely to report severe complaints of symptom frequency, intensity, and subsequent activity limitations.[22] In coronary artery disease, females reported atypical symptoms, such as jaw pain, shoulder pain, arm pain, nausea, fatigue, dyspnoea, and sweating, more frequently than men, rather than angina, a fact explained by a different sex-specific pathophysiology of acute coronary syndrome.[23]

To this end, Wu X et al.[24] conducted a longitudinal cohort study on patients admitted to the hospital for severe COVID-19, and examined them at 3 months, 6 months, 9 months, and 12 months after hospital discharge. The full lung assessment showed that females have a higher risk than males of persistent lung diffusion impairment.[24,25]

COVID-19 is a heterogenic, multi-systemic disease, with pneumonia being the dominant clinical manifestation. However, myocardial involvement has been demonstrated with imaging techniques, such as Echocardiography and Cardiac Magnetic Resonance imaging, both in the acute phase and many months after the onset of COVID disease, but these studies did not present sex-disaggregated data.[26,27] Females might show a later improvement in both pulmonary and cardiac function, but further studies are needed on this topic.

Lastly, it cannot be excluded that different reasons prompted males and females to participate in a multidisciplinary evaluation after SARS CoV-2 infection: Males may

have participated due to a history of critical illness, whereas females may have participated due to the experience of persistent symptoms.

Among the determinants of persistent symptoms, we demonstrated an inverse correlation between age and certain symptoms, including fatigue, chest pain, and palpitations, suggesting that the younger the patients, the more they reported symptom persistence. One explanation could be related to cerebrovascular ageing, older patients could be less symptomatic due to their deteriorating cognitive status and, hence, a potential reduction in symptom perception. However, our results disagree with other studies that showed a direct relationship between age and symptom persistence.[15,16]

CRDs were the only comorbidities we found correlated to Long-COVID; CRDs were predictors of persistent dyspnoea, which was also related with BMI.

Certain symptoms in the acute infection, such as dyspnoea, chest pain, palpitations, and myalgia, were powerful determinants of the persistence of the same symptoms in the chronic phase.

In contrast, Long-COVID was not associated with the severity of the infection based on the need for oxygen supplementation, and/or intensive care, or different pharmacological approaches to this disease amongst males and females. It should also be emphasized that, unlike coronary heart disease where females are under-treated compared to males, our study demonstrates the equality of treatment between the two sexes with regards to acute COVID-19 infection.

This study has some limitations. As with the most of the literature available on Long-COVID, the sample selection was not random and may be biased. Despite these limitations, our study has important strengths. The main one is the wide spectrum of

clinical features of COVID-19 patients who presented with mild to severe disease, which reflects the heterogeneity of SARS-CoV-2 infection.

Conclusions

In conclusion, COVID-19 is a clear example of the need for a sex- and gender informed clinical approach in the treatment of this disease. Higher mortality in males as compared to females worldwide has been demonstrated in the acute phase *(Teidal A et al.[2] in the USA found that females had a 27% lower risk of in-hospital mortality when infected with SARS CoV-2. Di Stadio A et al.[5] in Italy obtained similar results, finding that the mortality ratio was 3:1, male to female)* but that females are more affected by Long-COVID syndrome.

Therefore, it is imperative to study the outcomes of the infection separately in both sexes.

There are still uncertainties about the optimal management of these patients. Patients may require multidisciplinary care involving the long-term monitoring of ongoing symptoms to identify potential complications.

Moreover, long term longitudinal studies are needed to fully understand the sex-related pathophysiology of the symptoms associated with Long-COVID; this research will be crucial to understanding the natural trajectory of Long-COVID in order to implement targeted treatment strategies and to prevent bias in treating males and females.

Authors' Contributions

GP, MG, MC, MA, and AC contributed to the conception and design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. GP drafted the manuscript. All authors critically revised the manuscript and gave final approval.

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Author Disclosure Statement

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TABLE 1. CHARACTERISTICS OF THE COVID-19 POPULATION (N=223)

Variable	*Total (223)*	*Female (n=89)*	*Male (n=134)*	*p value*
Age (years)	59 ± 13	57±13	60±13	ns
BMI (kg/m^2)	28±5	28±7	28±4	ns
HR (bpm)	73±12	76±12	71±12	<0.01
SBP (mmHg)	131±18	126±19	134±17	<0.01
DBP (mmHg)	84±9	82±9	85±9	ns
Smoking (n,%)	15 (7)	7 (8)	8 (6)	ns
Former smokers (n,%)	97 (43)	23 (26)	74 (55)	<0.001
Physical activity*				
sedentary	74 (33)	33 (38)	41 (31)	
occasional	65 (29)	23 (26)	42 (32)	
regular	82 (37)	31(36)	51 (38)	ns
Educational level**				
<11 years	89 (41)	34 (40)	55 (41)	
11-13 years (secondary school)	80 (37)	31 (36)	49 (35)	
>13 years (University)	49 (22)	20 (24)	29 (22)	ns
Marital status *				
Single/separated/divorced	48 (22)	19 (22)	29 (22)	
Married/cohabiting	160 (73)	59 (68)	101 (75)	
Widowed	13 (6)	9 (10)	4 (3)	ns
Job/profession*				

Farmer, cook	8 (4)	1(1)	7 (5)	
Health staff	38 (17)	23 (26)	15 (11)	
Manager, clerical support, trader	106 (48)	39 (45)	67 (50)	
Craft and related workers	49 (22)	11 (13)	38 (28)	
Unemployed, homemaker	20 (9)	13 (15)	7 (5)	<0.001
Comorbidities				
Hypertension (n,%)	96(43)	33 (37)	63 (47)	ns
DM (n,%)	27 (12)	10 (11)	17 (13)	ns
CAD (n,%)	17 (8)	5 (6)	12 (9)	ns
CRDs (n,%)	39 (17)	15 (17)	24 (18)	ns
Beta-blockers (n,%)	52 (23)	14 (16)	38 (28)	ns
Ace-inhibitors (n,%)	38 (17)	15 (17)	23 (17)	ns
ARB (n,%)	31 (14)	10 (11)	21 (16)	ns
Antiplatelet (n,%)	40 (18)	11 (12)	24 (18)	ns

Footnotes: data are expressed as mean ± standard deviation or number of subjects with corresponding percentage. ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRDs, chronic respiratory diseases; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, heart rate; SBP, systolic blood pressure. * Data available on 221 patients (F=87; M=134) ** Data available on 218 patients (F=85; M=133)

Table 2. COVID-19 severity

Variable	Total (223)	Female (89)	Male (134)	p value
Hospitalized patients (n,%)	161 (72)	56 (63)	106 (79)	=0.017
Ordinary regime admissions (n,%)	133 (85)	47 (84)	86 (81)	ns
Intensive Care Unit admissions (n,%)	28 (17)	9 (16)	19 (18)	ns
Oxygen therapy (n,%)	147(66)	47 (53)	100 (75)	=0.001
Mask (n,%)	93 (42)	28 (31)	65 (48)	=0.013
Noninvasive ventilation, CPAP (n,%)	31 (14)	14 (16)	17 (13)	ns
Invasive mechanical ventilation (n,%)	24 (11)	8 (9)	16 (12)	ns
CV Complications				
ACS (n,%)	1	-	1	ns
Angina (n,%)	5 (2)	-	5 (4)	ns*
Arryhthmia (n,%)	16 (7)	8 (9)	8 (6)	ns
Myocarditis (n,%)	-	-	-	-
Pericarditis (n,%)	3 (1)	2 (2)	1 (1)	ns
DVT (n,%)	3 (1)	1 (1)	2 (1)	ns
VTE (n,%)	14 (6)	2 (2)	12 (9)	ns
Hemodynamic instability (n,%)	14 (6)	4 (4)	10 (7)	ns

Footnotes: data are expressed as mean ± standard deviation, median (IQ range) or number of subjects with corresponding percentages. CV, cardiovascular; DVT, deep vein thrombosis; VTE, venous thromboembolism. Chest CT visual score in the total population. *Test di Fisher

TABLE 3. COVID-19 THERAPY

Variable	*Total (223)*	*Female (89)*	*Male (134)*	*p value*
Antibiotics (n,%)	198 (88)	77 (87)	121 (90)	ns
Hydroxycloroquine (n,%)	125 (56)	46 (52)	79 (59)	ns
Colchicine (n,%)	29 (13)	11 (12)	18 (13)	ns
Antivirals *(lopinavir/ritonavir or darunavir/cobicistat)* (n,%)	94 (42)	30 (34)	64 (47)	=0.077
Biologics *(Tocilizumab or Sarilumab)* (n,%)	17 (8)	5 (6)	12 (9)	ns
Systemic corticosteroids (n,%)	106 (47)	49 (55)	57(42)	=0.07
LMWH - prophylactic dose (n,%)	115 (51)	50 (56)	65 (48)	ns
LMWH - therapeutic dose (n,%)	39 (17)	10 (11)	29 (21)	ns

Data are expressed as number of subjects with corresponding percentages

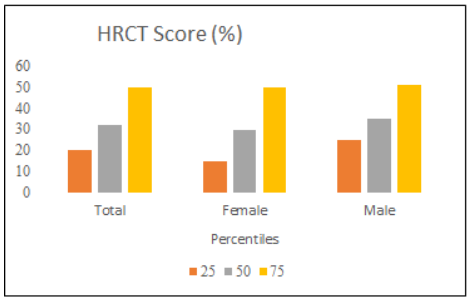
TABLE 4. FACTORS INDEPENDENTLY RELATED TO LONG COVID-19: MULTIPLE REGRESSION ANALYSIS.

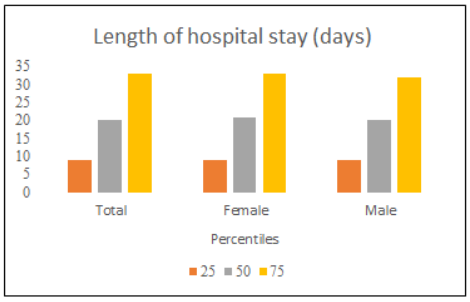
	Variables	*OR*	*p value*	*95%CI*
Dyspnoea	Sex	2.357	0.023	[1.124; 4.944]
	BMI	1.194	0.000	[1.092; 1.307]
	Dyspnoea	2.602	0.021	[1.152; 5.877]
	Cough	2.165	0.033	[1.062; 4.412]
	CRDs	3.977	0.021	[1.223; 12.932]
Fatigue	Sex	6.726	0.000	[2.349; 19.263]
	Age	0.958	0.025	[0.923; 0.995]
	Weight loss	0.222	0.005	[0.078; 0.636]
Chest Pain	Sex	2.046	0.048	[1.006; 4.158]
	Age	0.963	0.019	[0.934; 0.994]
	Chest Pain	4.035	0.000	[1.957; 8.320]
Palpitations	Sex	2.307	0.020	[1.142; 4.658]
	Age	0.969	0.051	[0.938; 1.000]
	Palpitations	6.520	0.000	[3.028; 14.042]
Myalgia	Myalgia	3.228	0.003	[1.497; 6.959]
Cough	Hospitalization	0.159	0.000	[0.56; 0.446]
Sleep disturbance	Sleep disturbance	3.942	0.014	[1.324; 11.738]

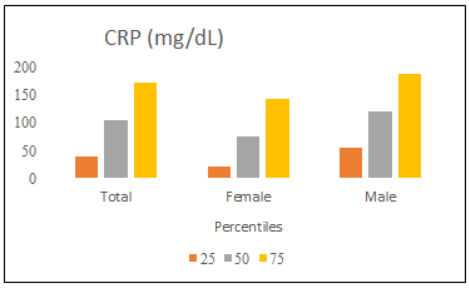
Physical Activity	0.262	0.011	[0.094; 0.731]
CPAP	0.204	0.044	[0.043; 0.956]
Headache	2.700	0.044	[1.028; 7.086]

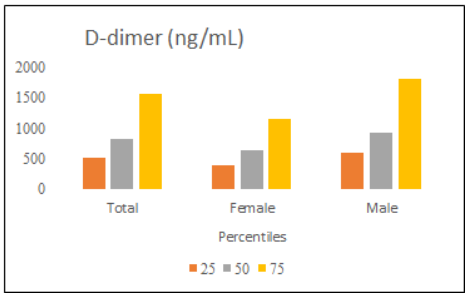
Footnotes: OD, odds ratio

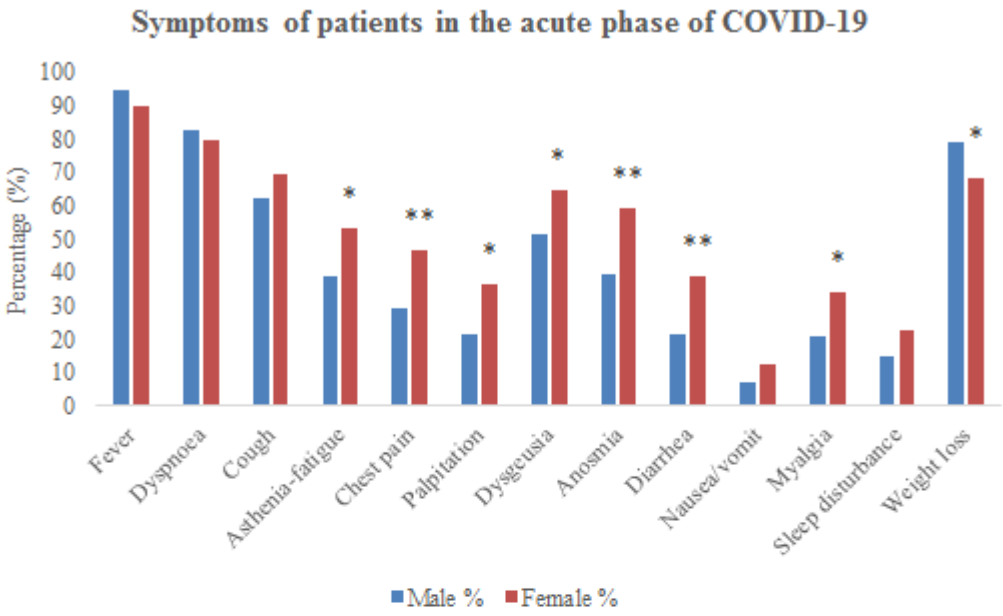
Distribution in percentiles for length hospital stay, HRCT Score, CRP and D-Dimer

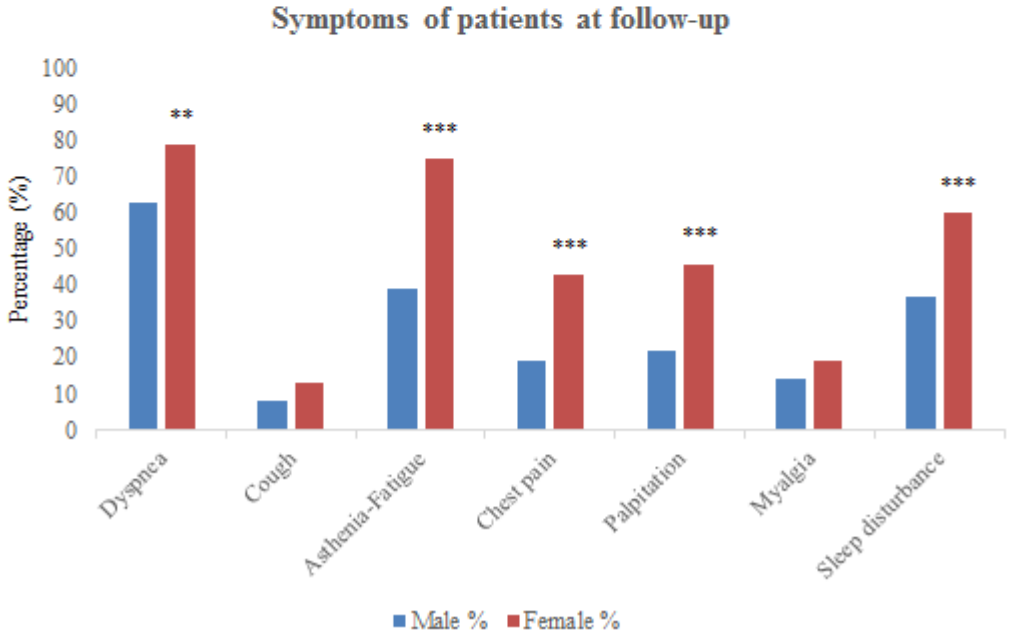


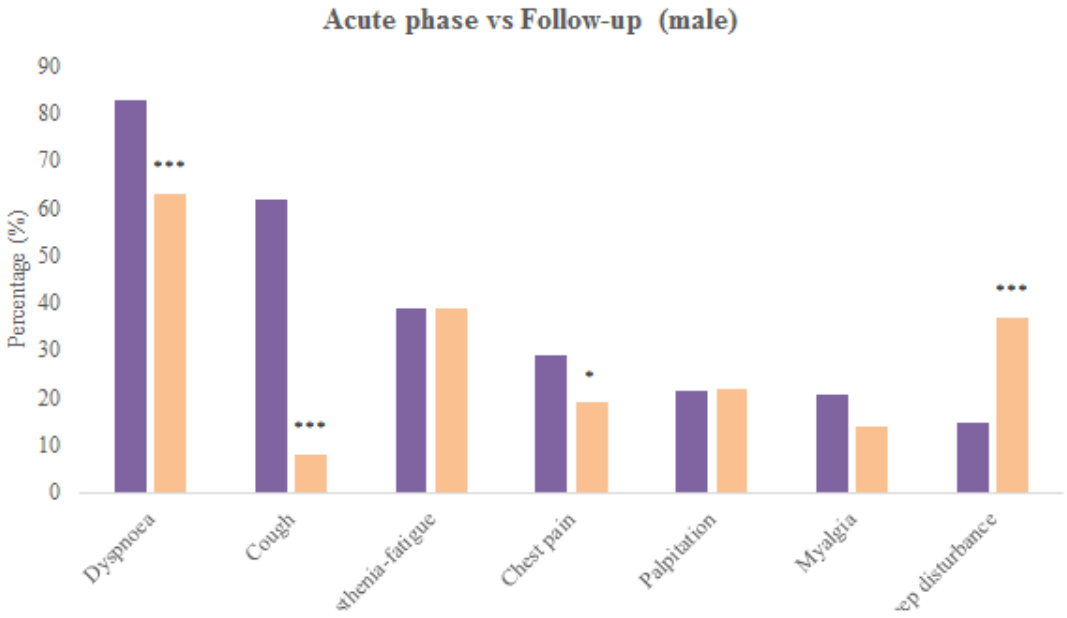







Symptoms of patients in the acute phase of COVID-19
Percentage (%)
100
90
80
70
60
50
40
30
20
10
0
Fever
Dyspnoea
Cough
Asthenia-fatigue
Chest pain
Palpitation
Dysgeusia
Anosmia
Diarrhea
Nausea/vomit
Myalgia
Sleep disturbance
Weight loss
Male %
Female %


Symptoms of patients at follow-up
Percentage (%)
100
90
80
70
60
50
40
30
20
10
0
Dyspnea
Cough
Asthenia-Fatigue
Chest pain
Palpitation
Myalgia
Sleep disturbance
Male %
Female %


Acute phase vs Follow-up (male)
Percentage (%)
90
80
70
60
50
40
30
20
10
0
***
***
*
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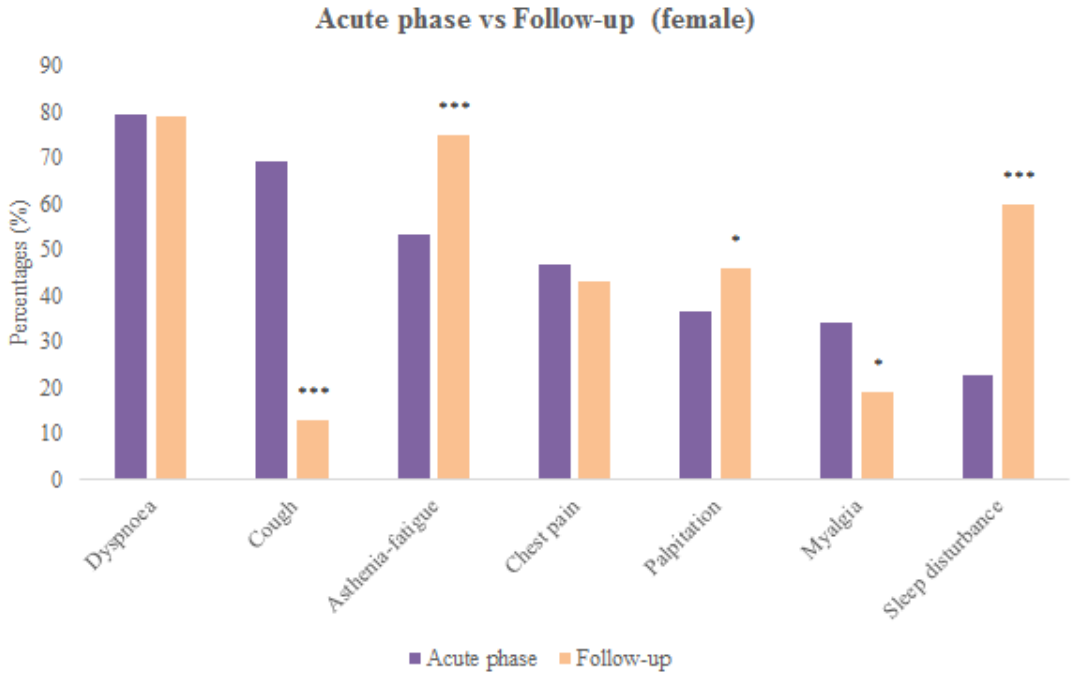
Dyspnoea
Cough
sthenia-fatigue
Chest pain
Palpitation
Myalgia
ep disturbance


Acute phase vs Follow-up (female)
Percentages (%)
90
80
70
60
50
40
30
20
10
0
***
***
*
*
***
Dyspnoea
Cough
Asthenia-fatigue
Chest pain
Palpitation
Myalgia
Sleep disturbance
Acute phase
Follow-up