Clinical presentation and pulmonary function tests in post-acute COVID-19 patients

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Aims. The study analysed post-acute COVID-19 symptoms and the pulmonary function test (PFT) results in patients surviving the native strain of the virus.
Methods. The study was prospective; the inclusion criteria were positive PCR test for SARS-CoV-2 and age 18–100. Exclusion criteria were active respiratory infection, known or suspicious pre-existing pulmonary disease, cardiac failure, recent or acute pulmonary embolism, anaemia, and neuromuscular diseases. The recruitment period was 1st March 2020 – 25th December 2020. The initial examination was performed 4–12 weeks after the disease onset. All subjects underwent physical examination, anamnesis, chest x-ray and PFT.
Results. The study involved 785 subjects (345 male) mean age 53.8 (SD 14.6). The disease severity groups were: mild (G1), moderate (G2) and severe/critical (G3). Anosmia was present in the acute disease phase in 45.2% of G1 patients, but only in 4.5% of G3 patients. Dyspnoea occurred frequently in more severe groups (40%, 51.8% and 63.7% for G1, G2 and G3 respectively), while cough and fatigue showed no relationship to disease severity. Females were more likely to experience persistent symptoms. PFT results were significantly decreased in more severe groups compared to the mild COVID-19 patients, diffusing capacity was 86.3%, 79% and 68% of predicted values in G1, G2 and G3 respectively.
Conclusion. Anosmia during the acute phase was associated with mild disease, persisting dyspnoea was more frequent after more severe COVID-19. Females tended to have persisting symptoms in post-acute phase more frequently. PFT results showed decrease with disease severity.

Key words: COVID-19, post-acute phase, clinical presentation, pulmonary function tests

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INTRODUCTION

Patients with COVID-19 experience a wide range of symptoms during the acute course, ranging from mild such as cough, sore throat, malaise, fever, headache, muscle pain, nausea, vomiting, diarrhoea, and anosmia to warning symptoms such as dyspnoea and signs of respiratory failure[1]. However, overcoming the infection often does not lead to complete relief and many patients in the so-called post-acute COVID-19 period (more than 12 weeks after the acute illness) have various persistent difficulties. While some symptoms, such as anosmia, may be of prognostic significance in acute phase of the infection[2], the presence of post-acute COVID-19 symptoms and their relationship to the consequences of the disease are still under investigation. Over the 2-year course of the COVID-19 pandemic, there are now available data on post-acute patients available from different periods of the pandemic (including probably different coronavirus mutations and various patient populations). A significant proportion of patients required hospitalization, and after discharge, many of them experienced so-called post-discharge syndrome including, for example, cough, shortness of breath and joint pain[3,4]. Data from the United Kingdom and Italy show more frequent post-discharge syndrome rates than data from Wuhan in China, but these include different patient populations and cohort sizes[5]. There are also indications that the prevalence of persistent cough decreases significantly from the post-acute period to 1 year after infection in survivors of COVID-19 pneumonia[6-8]. Importantly, the causality and associations between symptoms, radiological abnormalities and lung function impairment remain under debate. The persistence of radiological abnormalities in patients was not clearly associated with the occurrence of symptoms and, conversely, only a minority of patients with persistent shortness of breath and cough had pathology on chest X-rays or impaired lung function[9]. Acute disease severity may also play a role in the frequency of persistent abnormalities: up to 40% of patients with pneumonia had impaired diffusion

capacity for carbon monoxide in the post-acute period[10-12]. Pulmonary function testing showed a two to three times higher occurrence of restrictive ventilatory disorders compared to obstructive disorders, but there is considerable heterogeneity between studies in the evaluation of lung functions[9-10]. In addition, the proportion of pre-existing pulmonary disease, whether already treated or previously unrecognized, as well as the impact of smoking on the subjective difficulties and measurable outcomes, has not been fully elucidated. Furthermore, there is growing evidence that a more severe course of the disease leads to a longer persistence of antibody production, but their role and relationship to other outcomes is also unknown[13]. Lastly, despite valuable data from Western and Southern Europe, sufficient data on the post-acute patients from Central and Eastern Europe are lacking. Therefore, the present study aimed to analyze the relationships between symptoms, lung functions, radiological changes, and antibody production, considering also gender differences, in a group of patients from the Czech Republic.

METHODS

Subjects included in the study were consecutive patients of the Department of Respiratory Diseases and Tuberculosis University Hospital Olomouc, the study had a prospective design. The inclusion criteria for subject involvement were positive PCR test for SARS-CoV-2, ability to perform pulmonary function tests and age 18–100. All patients signed an informed consent to follow-up at the outpatient clinic. Exclusion criteria were active respiratory infection, known or suspicious pre-existing pulmonary disease, known or suspicious cardiac failure, unconfirmed diagnosis of COVID-19, recent or acute pulmonary embolism (up to 3 months before the examination), moderate or severe anaemia, and neuromuscular diseases. The recruitment period was set by the date of the positive PCR test for the virus in relation to the dominance of the Wuhan (non-mutated) SARS-CoV-2 variant, i.e., from 1st March 2020 until 25th December 2020 when the first subjects with so called British mutation (alpha variant) were identified in the Czech Republic. The initial examination was performed 4–12 weeks after the first positive PCR result. All subjects had completed physical examination, detailed anamnesis, antero-posterior chest x-ray, pulmonary function tests and selected laboratory tests.

Pulmonary function test measurements were done in concordance with actual European respiratory society/American thoracic society guidelines[14]. Body plethysmography MasterScreen by Jaeger® was used for pulmonary function testing, using software SentrySuiteTM Version 2.19 by CareFusion for data retrieval. The diffusing capacity for carbon monoxide (TLCO) was measured by the dilution method using Helium as an inert gas. In patients with significant reduction of diffusing capacity (under 60% of predicted values), or other signs of possible interstitial damage (based on the chest x-ray or auscultation finding), a high-resolution computed tomography (HRCT) scan was performed. The pathological changes on the HRCT were further described as alveolar (ground glass opacities or parenchymal condensations) or interstitial (reticulations, traction bronchiectasis or honey combing) (ref.[15]).

The laboratory tests included ion levels (Na, K, Cl, Ca, Mg), renal and liver function tests, blood count including white blood cell differential, coagulation screening and serology for the SARS-CoV-2 antibodies levels (IgG and IgM classes).

The subjects were divided into 3 groups according to the three severity groups based on ERS guidelines[16]: Group 1 (asymptomatic and mild course) included patients without the need of hospital admission, Group 2 (moderate) included patients requiring hospitalization and low-flow oxygen support, and finally the Group 3 included patients requiring high-flow oxygen support, non-invasive or invasive ventilation support or extra-corporeal membrane-oxygenation.

The data were analysed using the IBM SPSS Statistics version 23 (Armonk, NY: IBM Corp.). Kruskal-Wallis test and post-hoc Mann-Whitney test with Bonferroni correction were used for inter-group comparison. ANOVA dispersion analysis was used for age comparison. The Mann-Whitney U test was used to assess the difference in qualitative parameters between the sexes.

The qualitative parameters in groups according to the disease severity were compared using Chi-square test or Fisher's exact test. The normality of data distribution was assessed by Shapiro-Wilk test. All tests were performed at the alpha level 0.05.

The study was in concordance with latest Helsinki declaration and was approved by the local Ethics committee; decision number EK 98/21.

RESULTS

845 patients were screened for eligibility in the study period, 60 of whom were excluded (2 due to neuromuscular disease, 10 due to acute or recent pulmonary embolism, 10 due to acute respiratory infection, 38 due to pre-existing respiratory disease). In total 785 subjects (345 male) mean age of 53.8 (SD 14.6) were included. None of the patients had confirmed reinfection with SARS-CoV-2 in the time of the initial visit. See Table 1 for the study group description. For inter-group comparison in the total sample, see Table 2. Table 3 provides comparison between the sexes for each disease severity group. Notably, anosmia was present during the acute stage of the disease in 45.2% of patients in Group 1, while only in 4.5% of Group 3 patients. The data show a higher percentage of men in the more severe disease groups. Similarly, age significantly correlated with disease severity with a mean age of 63 in Group 3 compared to 47.5 in Group 1 and 57.6 in Group 2. Considering the symptoms, only dyspnoea occurred more frequently in more severe groups, while cough and fatigue were not significantly correlated with the disease severity. On the other hand, the pulmonary function tests results were significantly lower (vital capacity, forced expiratory volume in 1s and parameters of lung diffusion) in

Table 1. Overall study groups characteristics.

	Group 1	Group 2	Group 3	*P*
n	440	166	179	–
Males	161 (36.6%)	82 (49.4%)	102 (57.2%)	**< 0.0001**
Age	47.5 ± 13.3	57.6 ± 12.6	63.0 ± 12.5	**< 0.0001**
Smoking	44 (10.6%)	9 (5.8%)	8 (5%)	0.08
Dyspnoea	40%	51.8%	63.7%	**< 0.0001**
Cough	30.9%	36.7%	26.3%	0.109
Anosmia	199 (45.2%)	33 (19.9%)	8 (4.5%)	**< 0.0001**
Fatigue	86 (19.5%)	44 (26.5%)	47 (26.3%)	0.075
Dyspepsia	79 (18.0%)	27 (16.3%)	30 (16.8%)	0.864
VC (%pred)	105.2 (66–143)	98.9 (59–149)	92.2 (34–141)	**< 0.0001**
FEV1 (%pred)	105.0 (66–154)	101 (48–148)	94.3 (31–150)	**< 0.0001**
TLCO (%pred)	86.3 (60.2–130)	79 (39.4–119)	68 (23–113)	**< 0.0001**
AC	35 (8.0%)	46 (27.7%)	72 (40.2%)	**< 0.0001**
IC	9 (2.0%)	13 (7.8%)	38 (21.2%)	< 0.0001

%pred, % of predicted values; VC, vital capacity; FEV1, forced expiratory volume in 1s; TLCO, total diffusion capacity for carbon monoxide; AC, alveolar changes; IC, interstitial changes (HRCT); variables with $P<0.05$ did not violate normality. Group 1 = mild, Group 2 = moderate, Group 3 = severe/critical.

Table 2. Inter-group comparison (post-hoc tests).

Post-hoc tests	Group 1 versus 2	Group 1 versus 3	Group 2 versus 3
Males	**0.012**	**< 0.0001**	0.475
Age	**< 0.0001**	**< 0.0001**	**0.0005**
Dyspnoea	**0.027**	**< 0.0001**	0.077
Anosmia	**< 0.0001**	**< 0.0001**	**< 0.0001**
IC	**0.003**	**< 0.0001**	**0.003**
AC	**< 0.0001**	**< 0.0001**	0.118
VC (% pred)	**< 0.0001**	**< 0.0001**	**0.003**
FEV (% pred)	**0.023**	**< 0.0001**	0.063
TLCO (% pred)	**< 0.0001**	**< 0.0001**	**< 0.0001**
KCO (% pred)	1.000	**0.005**	0.065
IgG antibodies	**< 0.0001**	**< 0.0001**	1.000
IgM antibodies	**< 0.0001**	**< 0.0001**	0.794

%pred, % of predicted values; VC, vital capacity; FEV1, forced expiratory volume in 1s; TLCO, total diffusion capacity for carbon monoxide; KCO, transfer coefficient for carbon monoxide; AC, alveolar changes; IC, interstitial changes (HRCT); all tests were done at an alpha level of 0.05.

more severe groups compared to the mild COVID-19 patients. Additionally, both interstitial and alveolar changes on HRCT were more common in more severe forms of the disease. The antibody levels (in both measured classed – IgG and IgM) were significantly higher in more severe forms (see the Tables 2 and 3 and Fig 1 and 2).

Comparison between the sexes revealed a significantly higher prevalence of exertional dyspnea in females versus males in Group 1 (44.4% vs 32.3%, respectively), no difference between the sexes was observed in Groups 2 and 3. Persisent cough was more prevalent in females than in Group 1 (35.1% in females vs 23.6% in males), while the opposite was observed in Group 2 (46.3% in males vs 27.4% in females). Fatigue was statistically significantly more prevalent in females in Groups 2 and 3, but not in Group 1 where only a trend towards statistical significance was found (21.9% of females vs. 15.5% in males, $P=0.106$). The analysis of pulmonary function test results revealed a consistently higher vital capacity (expressed as a percentage of predicted value) in females in all severity groups. Significant difference in lung diffusion capacity for carbon monoxide (TLCO; expressed as a percentage of predicted value) was observed only in Group 1 where TLCO was significantly higher in males ($P<0.0001$). While there were no differences between sexes in the perception of dyspnoea in Groups 2 and 3, the dyspnoea in the post-acute phase of COVID-19 was reported significantly more frequently by women in Group 1 (mild course of the disease).

Comparing the sex differences in the correlating disease severity groups we found several interesting facts. Exertional dyspnoea was more common in females in Group 1 (44.4% in females vs. 32.3% in males), while in other groups there were no significant differences between the sexes. Persisting cough was more common in females in Group 1 (35.1% in females vs.23.6% in males), but interestingly cough was more common in males in Group 2 (46.3% in males vs. 27.4 in females). The only consistent

Table 3. Statistics by group and sex.

	Males	Females	*P*
Disease severity		**Mild**	
n	161 (36.6%)	279 (63.4%)	–
Age	47.1 ± 14.1	47.7 ± 12.8	0.676
Smoking	18 (11.5%)	26 (10.0%)	0.231
Dyspnoea	52 (32.3%)	124 (44.4%)	**0.012**
Cough	38 (23.6%)	98 (35.1%)	**0.012**
Anosmia	66 (41.0%)	133 (47.7%)	0.175
Fatigue	25 (15.5%)	61 (21.9%)	0.106
Dyspepsia	25 (15.5%)	54 (19.4%)	0.314
VC (%pred)	101.1 (74–138)	108.5 (66–143)	**< 0.0001**
FEV1 (%pred)	102.9 (73–139)	105.3 (66–154)	0.293
TLCO (% pred)	90.3 (61.5–130)	80.7 (60.2–112)	**< 0.0001**
AC	11.8%	11.3%	0.900
IC	3.6%	2.6%	0.728
IgM antibodies (AU)	1.6 (0.06–99.6)	1.02 (0.06–50.8)	**0.035**
IgG antibodies (AU)	57 (3.8–400)	48 (3.8–400)	0.699
Disease severity		**Moderate**	
n	82 (49.4%)	84 (50.6%)	–
Age	57.6 ± 12.6	56.7 ± 12.3	0.385
Smoking	7 (9.2%)	2 (2.5%)	0.010
Dyspnoea	43 (51.4%)	43 (51.2%)	0.872
Cough	38 (46.3%)	23 (27.4%)	**0.011**
Anosmia	17 (20.7%)	16 (19.0%)	0.786
Fatigue	16 (19.5%)	28 (33.3%)	**0.044**
Dyspepsia	11 (13.4%)	16 (19.0%)	0.326
VC (%pred)	92.7 (58–130)	104.7 (70–149)	**< 0.0001**
FEV1 (%pred)	98.7 (48–132)	101.9 (67–148)	0.073
TLCO (% pred)	79.0 (38–119)	76.2 (40–110)	0.110
AC	37.3%	38.7%	0.872
IC	15.3%	6.5%	0.118
IgM antibodies (AU)	7.4 (0.17–99.6)	3.4 (0.05–104)	**0.0004**
IgG antibodies (AU)	133 (3.8–400)	127 (3.8–400)	0.728
Disease severity		**Severe**	
n	102 (57.0%)	77 (43.0%)	–
Age	63.3 ± 12.5	62.5 ± 12.5	0.650
Smoking	3 (3.4%)	5 (6.9%)	0.394
Dyspnoea	67 (65.7%)	47 (61.0%)	0.522
Cough	26 (25.5%)	21 (27.3%)	0.788
Anosmia	3 (2.9%)	5 (6.5%)	0.292
Fatigue	18 (17.6%)	29 (37.7%)	**0.003**
Dyspepsia	12 (12.8%)	17 (22.1%)	0.098
VC (%pred)	85.3 (43–140)	97.5 (56–135)	**< 0.0001**
FEV1 (%pred)	91.9 (31–145)	98.6 (61–150)	**0.002**
TLCO (% před)	67.9 (23–113)	67.9 (26–112)	0.490
AC	55.7%	44.4%	0.183
IC	30.4%	22.2%	0.275
IgM antibodies (AU)	6.27 (0.14–111)	4.06 (0.08–90)	0.162
IgG antibodies (AU)	161 (5.7–400)	152 (14.3–400)	0.246

%pred, % of predicted values; VC, vital capacity; FEV1, forced expiratory volume in 1s; TLCO, total diffusion capacity for carbon monoxide; AC, alveolar changes; IC, interstitial changes (HRCT); P<0.05 = statistically significant difference between the sexes.

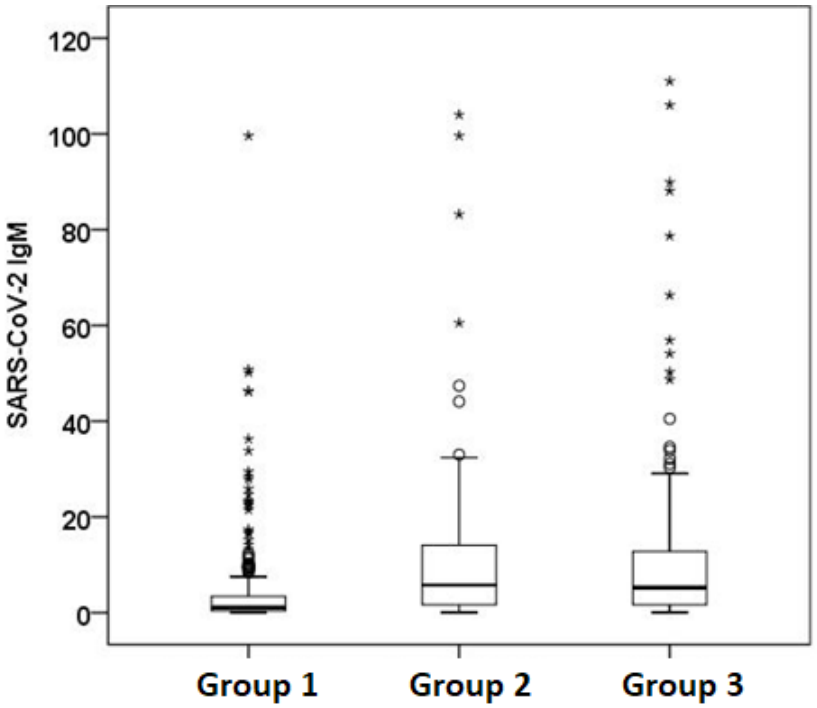

Fig. 1. The antibody levels distribution (AU in IgM class), the levels were significantly higher in moderate and severe disease compared to the mild COVID-19 group (Group 1).

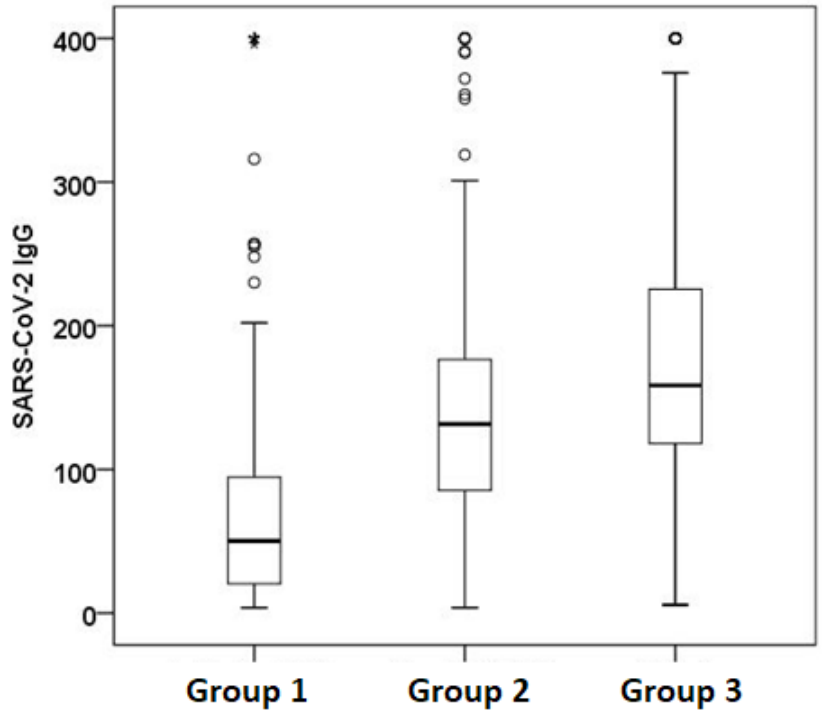

Fig. 2. The antibody level distribution (AU in IgG class), the levels were significantly higher in moderate and severe disease compared to the mild COVID-19 group (Group 1).

persisting symptom was fatigue, which was more common in females in all groups, but in Group 1 where a possible trend was found, but without significant statistical significance (21.9% of females vs. 15.5% in males, *P*=0.106). There were also differences in the pulmonary function test results, namely vital capacity was consistently higher in females in all disease severity groups. There were no significant differences in total lung diffusion capacity (TLCO). Only in Group 1 we found higher TLCO in the male subgroup. While there were no differences in the perception of dyspnoea in the moderate and severe course, in patients with a mild course, dyspnoea occurred more frequently in the post-acute COVID-19 period in women.

DISCUSSION

This study has provided a comprehensive view of patients with post-acute COVID-19 syndrome, including clinical presentation, lung function, antibody levels and radiological changes. In accordance with the literature, we recorded the presence of anosmia (in the acute stage of the disease) mainly in patients with a mild course of the disease, while in patients with a severe course, this symptom was rare[17]. In contrast, patients with severe acute illness had more severe dyspnoea, poorer lung function, more persistent changes in lung HRCT, and higher antibody levels in the post-acute period. This group was characterized by higher prevalence of men and significantly higher age, which is in agreement with the proven risk factors for severe disease such as age, male gender, non-white ethnicity, and comorbid chronic lung disease[18]. Differences in the symptoms of the post-acute phase of COVID-19 were observed between the sexes and disease severity groups. While there were no differences in the perception of dyspnoea in the moderate and severe course, in patients with a mild course, dyspnoea occurred more frequently in the post-acute COVID-19 period in women. The strongest association to either sex was observed in the persistent fatigue, which was consistently more frequently reported by women, the difference being statistically significant in the two more severe disease groups, while showing a trend in the mild disease group. Fatigue is a common symptom reported in several studies and is in the range from 29.5% of patients at 3-month follow-up[19] to 63% at 6-month[20]. Fatigue is a complex, common, and unpleasant consequence of COVID-19 and is often a part of chronic fatigue syndrome (CFS) (ref.[21]). We have no clear explanation for the association of fatigue as a post-COVID-19 symptom with the female sex. An interesting finding from the countries of Central Eastern Europe (CEE) was recently provided by authors from Croatia, who assessed the Functional status of patients with the Post-Covid-19 Functional Status (PCFS) scale. Fatigue was one of the most reported symptoms and in this study the PCFS score was higher in women (more severe impact of the disease) (ref.[22]). Other studies showed that female sex can be a risk factor for developing long COVID-19 and a higher incidence of COVID-19 symptoms in women and young adults[23-24].

Interestingly, there are better PFT results in female subjects. Vital capacity is significantly higher and consistently through all severity groups. This aside there was a larger proportion of females with dyspnoea and fatigue. This might be due to higher sensitivity to minor reduction in respiratory function. Skala et al.[25] found in their interim analysis of post-COVID-19 patients that the reporting of symptoms was more frequent in patients with higher levels of anxiety, especially in females. In their study, the pulmonary involvement was found mostly in hospitalized subjects where 77% of patients had significant pulmonary changes.

The strengths of our study were the number of examined patients and the complexity of the examinations carried out, the use of unique data from the Central and Eastern European region and especially the analysis of sex differences, which proves to be very important in relation to the post-acute COVID-19 course. The limitations of this study include single-centre experience and only assessing patients with the Wuhan variant of SARS-COV-2 infection (non-mutated strain); therefore, we cannot evaluate and generalize the symptoms and consequences to other variants. Moreover, the subjects had no mutation analysis; therefore we cannot be absolutely certain that all of them were infected by the native strain of the virus, however during the recruitment period there were no notable mutations identified in the Czech Republic. In the future, we also plan to analyse the data on patients in our population infected with alpha, delta and omicron variants and compare the data on the post-acute COVID-19 course between the individual mutations. We also plan to provide our complete dataset for other researchers.

CONCLUSION

The presented study analysed the clinical presentation and objective findings in the post-acute COVID-19 patients. The anosmia at the acute phase was associated with mild course of the disease, while the opposite was observed in persisting dyspnoea that was reported more frequently in the more severe disease groups. Female sex seems to be a risk factor for persisting symptoms in post-acute phase. PFT results are decreasing with the disease severity. The antibody levels tend to increase with the disease severity. Our findings are in concordance with the current literature and may be used for further comparisons with other variants/mutations of the virus.

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PP: participated on data analysis, manuscript preparation, and language correction.

Conflicts of interest statement: Authors declare no conflict of interest regarding this manuscript.

Ethics approval: The study was approved by Palacky University, Czech Republic, Ethics Committee with decision number EK 98/21.

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