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Prolonged corticosteroid therapy and lung abnormalities in patients after severe COVID-19 pneumonia

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Abstract. *Background:* Some of the hospitalized patients after severe COVID-19 pneumonia experience persistent radiological pulmonary sequelae, respiratory symptoms, and decreased lung function despite optimal treatment according to the guidelines. Because of immune dysregulation in COVID-19 there are indications that prolonged corticosteroids could be considered in treating patients for persistent radiological sequelae and respiratory symptoms. *Objectives:* to investigate lung function and lung sequelae on high-resolution CT (HRCT) in COVID-19 patients who were treated with glucocorticoid therapy in two dose regimens with a control group of patients who did not receive additional glucocorticoid therapy. *Methods:* In this prospective cohort research patients discharged from the hospital after being hospitalized because of severe COVID-19 pneumonia received corticosteroid therapy in two dose regimens: for 14 days and for 3 months. The control group of patients did not receive additional corticosteroid therapy. Lung function, post-COVID-19 symptoms, and lung abnormalities on HRCT scans were analyzed in three months follow-up. *Results:* Patients who received prolonged corticosteroid therapy for three months did not have better HRCT findings of lung abnormalities, lung function, or symptoms recovery in comparison to the patients with 14 days of therapy and the control group of patients. Onwards, the control group had significantly fewer dyspnea symptoms (Chi-square test, p=0,04) and higher DLCO (Kruskal Wallis test, p=0,03). *Conclusions:* Supplementary corticosteroid therapy for patients after severe COVID-19 pneumonia with lung abnormalities did not improve lung function, symptoms or lung lesions on CT.

Key words: CT scan, COVID-19, pneumonia, viral, spirometry, capacity, pulmonary diffusing, lung function tests, corticosteroid, dyspnea

Introduction

SARS-CoV-2 infection pandemic caused difficult challenges for healthcare systems worldwide. The occurrence of the B.1.1.7 variant (Alpha, first identified in the United Kingdom) in February 2021 caused the third pandemic wave in Croatia, with 113 168 COVID-19 cases in Croatia until May 2021 (1). Results of the autopsy research of the COVID-19 patients who have died of pneumonia revealed diffuse alveolar damage in the lungs (2). Among the associated pulmonary pathologies of COVID-19 infection most common were pneumonia, thromboembolism, and lung fibrosis (3). Severe COVID-19 pneumonia is known for a prolonged duration of symptoms, with a higher frequency of severe clinical picture in males, older age, and in patients with more comorbidities such as diabetes mellitus, obesity, and arterial hypertension (4). Type 2 diabetes mellitus,

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coronary artery disease, interstitial lung disease, and BMI >35kg/m2 were significant risk factors for oxygen weaning failure and prolonged convalescence in patients with COVID-19 who are 50 years or older according to Ray et al. (5). The rate of development of lung fibrosis after COVID-19 atypical pneumonia and long-term prognosis is still undetermined (6). One year of follow-up and evaluation of CT lung sequelae demonstrated that residual CT abnormalities were common in hospitalized COVID-19 patients, in particular fibrotic changes (7). Post-COVID-19 lung disease pathophysiology suggests similarity to idiopathic pulmonary fibrosis (8,9). At this point, there are no established guidelines for the therapy of post-COVID-19 interstitial lung disease, while antifibrotic and immunosuppressive treatments are being investigated (10,11). Some of the hospitalized patients with severe COVID-19 disease even in mild physical exertion 20 days after symptoms onset experienced significant fall in peripheral Sp02 (below 90%) despite treatment according to the guidelines, and respiratory physiotherapy during hospitalization. In this study we have performed a detailed analysis of clinical data, compared the outcomes (lung function and CT findings), and the spectrum of post-COVID-19 symptoms in patients treated with corticosteroids post-discharge in two dose regimens compared to the control group at the follow-up appointment three months after discharge from the hospital. We emphasize that these three cohorts were patients with severe clinical picture and extensive lung lesions which led to a slower recovery than the majority of COVID-19 patients.

Methods

Study population

This study included adult patients with confirmed SARS-CoV-2 infection hospitalized in the Primary respiratory-intensive care center for treatment of patients with COVID- 19 disease in Dubrava University Hospital, Zagreb, Croatia, due to severe pneumonia and respiratory insufficiency from January to May 2021. COVID-19 (B.1.1.7 variant SARS-CoV-2) diagnoses were confirmed using a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay to test nasal and pharyngeal swab specimens. Study included patients with bilateral pneumonia who were treated with high-flow nasal oxygen (HFNO), mechanical ventilation (MV) or needed to be hospitalized for more than 14 days due to prolonged oxygen therapy with more than 20 days from the onset of symptoms. All patients received corticosteroid therapy during their hospitalization based on the RECOVERY study trial results (12) and other standard therapy for COVID-19. Exclusion criteria were former chronic lung disease, unstable cardiac disease, contraindications for prolonged corticosteroid therapy such as unregulated diabetes mellitus, unregulated arterial hypertension, severe osteoporosis, psychiatric disorders, body mass index 40 and above (13). Patients who did not take the therapy regularly were excluded from the study.

Study design

In this prospective cohort study during hospitalization the following interventions were performed and later analyzed: CT of the thorax, detailed clinical and medical history examination, and laboratory results. All three cohorts were well matched for their sex, age, comorbidities, and smoking status as demonstrated in Table 1.

On follow-up examination, three months later (±15 days), assessment of the mMRC dyspnea scale, HRCT, pulmonary function tests (spirometry and lung diffusing capacity for CO), BMI, smoking status, comorbidities, laboratory findings (complete blood count, CRP, D-dimers, basic biochemistry findings, HbA1c, ferritin, NT pro-BNP), and clinical symptoms (cough, shortness of breath, fatigue, or other) were obtained. The first group of patients was instructed to take prednisone 40 mg and to gradually taper the corticosteroid therapy within 14 days post-discharge (the recommended dose was 40 mg for 2 days, 20 mg for 2 days, 10 mg for 2 days, and 5 mg until the 14th-day post-discharge). The second group of patients was discharged with a prolonged corticosteroid therapy regimen with prednisone in dosage: 40 mg for 7 days, 20 mg for 14 days, and 10 mg until the follow-up examination. The control group of patients was given their regular therapy without additional corticosteroid treatment. All the groups were uniform in basic clinical and demographic characteristics (Table 1).

Computed tomography (CT) examinations

The initial CT examination was performed during hospitalization using a 128-detector CT device (Somatom Definition, AS Siemens), for assessment of lung parenchyma abnormalities. The follow-up

Table 1. Initial demographic and clinical data of patients with severe COVID-19 pneumonia and prolonged respiratory insufficiency.

Initial demographic and clinical data	All patients (n = 93)	Group I (corticosteroid therapy for 14 days) (n = 30)	Group II (prolonged corticosteroid therapy 3 months) (n = 44)	Control Group (n = 19)	P*
Age, median (IQR)	65 (59 - 73)	66 (60 - 73)	65 (59 - 72)	64 (50 - 76)	0,86†
Male gender n (%)	56 (60)	22 (73)	23 (52)	11 (58)	0,19
Female gender	37 (40)	8 (27)	21 (48)	8 (42)	
Non-smoker n (%)	54 (58)	23 (77)	31 (70)	0	0,83
Current smoker	5 (5)	0	3 (7)	2 (11)	
Ex-smoker	34 (37)	7 (23)	10 (23)	17 (89)	
Diabetes mellitus n (%)	16 (17)	5 (17)	10 (23)	1 (5)	0,24
Arterial hypertension n (%)	49 (53)	19 (63)	23 (52)	7 (37)	0,19
Hyperlipoproteinemia n (%)	15 (16)	4 (13)	10 (23)	1 (5)	0,24
Malignant disease n (%)	7 (8)	2 (7)	4 (9)	1 (5)	>0,99
Liver disease n (%)	3 (3)	1 (3)	0	2 (11)	0,08
St. post myocardial infarction n (%)	7 (8)	3 (10)	3 (7)	1 (5)	0,88
Hemoptysis n (%)	5 (5)	1 (3)	2 (5)	1 (5)	0,59
MEWS score	3 (1 - 4)	2,5 (1 - 4)	3 (2 - 4)	3 (1 - 5)	0,78†
Mechanical ventilation during hospitalization	5 (5)	1 (3)	3 (7)	1 (5)	0,85
HFOT	42 (45)	12 (40)	22 (50)	8 (42)	0,63

*Chi-square test; †Kruskal Wallis test.

HRCT examination was performed 3 months after discharge (+/- 15 days) using the standard HRCT protocol. The CT scoring system was developed for assessment of the type of predominant lung parenchyma changes due to COVID-19 pneumonia, as follows: 1. consolidation superimposed on ground-glass opacities (GGO), 2. predominantly crazy paving pattern, including other patterns (e.g.GGO, consolidation), 3. GGO predominantly, and 4. residual "fibrotic-like" abnormalities. Percentages of lung lesions were described as: <5%, 5 - 25%, 25 - 50%, 50 - 75%, and >75%. The results of the first CT and second HRCT findings were interpreted by the same thoracal radiologist. The interpretation of the CT scans, unfortunately, did not undergo a review process due to difficult conditions during the pandemic. Radiologist was blinded to the clinical course and the therapy given to the patient.

Pulmonary function tests

Spirometry and DLCO were measured with the ultrasonic EasyOne Pro spirometer. Measurements were performed according to the standardized recommendations (ERS/ATS) (14,15). All patients performed lung function tests three months post-discharge. One group of patients at this point had already finished the corticosteroid course, but the other group of patients was still using corticosteroid therapy (10 mg of prednisone therapy).

Dyspnea score

The modified Medical Research Council (mMRC) dyspnea scale was used to quantify the extent of dyspnea between categories 0 to 4 (16).

Statistical analysis

Categorical data are represented as absolute and relative frequencies. The differences in categorical variables were tested by Chi-square test. Numerical data were described by median and interquartile range. Differences in continuous variables for all three independent groups were tested by Kruskal-Wallis test (with 95% CI). All p values are double-sided. The level of significance was determined at Alpha = 0.05. Data analysis was conducted using the statistical

packages MedCalc® Statistical Software version 20.026 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) and SPSS 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results

93 patients were involved in this study. Group I consisted of 30 patients (treatment for 14 days), group II of 44 patients (treatment for three months), and the control group consisted of 19 patients. The median time from the onset of symptoms to hospitalization was 9 days (IQR: 6,0 - 12,0). The median age of the patients was 65 years (IQR 59 - 73), 56 (60%) of the patients were male gender, and 54 (58%) patients were never smokers. Median body mass index (BMI) was 28,4 (IQR 25,5 - 31,6). 49 (53%) of the patients had arterial hypertension and 16 (17%) had type 2 diabetes mellitus (Table 1). The median hospitalization period was 26 days (IQR 17,5 - 35,5). The detailed general information of patients is summarized in Table 1. Five (5%) patients were on mechanical ventilation during hospitalization and 42 (45%) on high-flow oxygen therapy (HFOT). The rest of the patients required oxygen therapy by face mask. There were no significant differences in received oxygen therapy between compared groups. All three groups of patients were well matched for laboratory findings and acid-base blood gas findings (Sp02, pC02, p02, pH) at baseline. Four of the patients were taking immunosuppressive therapy (one in control group, one patient in 14 days of corticosteroid therapy group, and 2 patients in three months of corticosteroids group). Bilateral diffuse CT abnormalities were present among all included patients. On initial CT scans consolidations (pattern 1) were found in 49 (53%) of all patients, crazy paving (pattern 2) in 24 (26%) patients, predominant GGO (pattern 3) in 18 (19%), and fibrotic-like reticulations (pattern 4) in 2 patients (2%). Example is presented on Figure 1 which represents CT scan with visible crazy paving, consolidation, and ground glass opacities. Figure 2 shows regression of lung lesions, with still visible discrete ground glass opacities after three months. Seventy participants performed the final HRCT analysis.

Table 2 demonstrates the regression of consolidations and crazy paving pattern over the three months period on control CT examinations in all three groups.

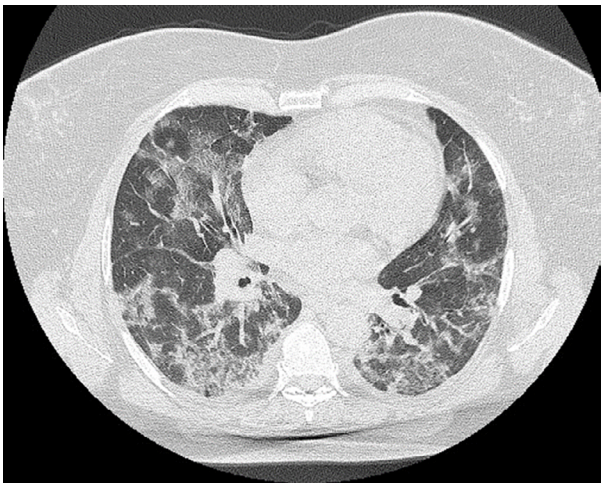

Figure 1. Example of typical CT imaging features for severe COVID-19 in 65-year-old male patient (during hospitalization) showing bilateral multifocal crazy paving pattern, ground-glass opacities, and posterior consolidation on the right side.

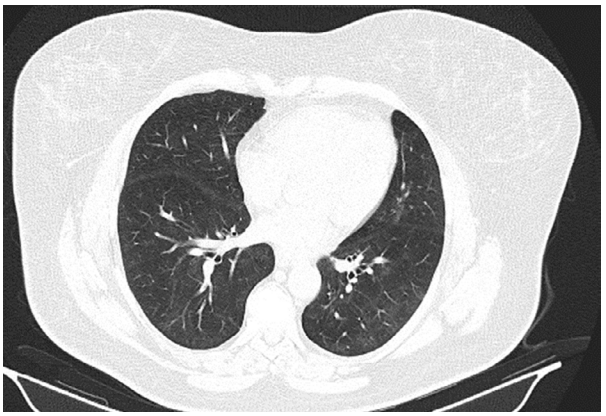

Figure 2. CT image demonstrates significant regression of bilateral COVID-19 lesions, with still visible ground-glass opacities in the same patient three months after discharge from the hospital.

On follow-up HRCT, ground glass opacities were seen in 21 (30%), and fibrotic-like lesions, which tended to increase were present in 46 (66%) patients (Table 2). GGOs and residual fibrotic-like lesions were predominant radiologic features on control scans in all three groups of patients. Patients were well matched for initial CT lung lesions type. There was no significant differences between CT type of lung lesions on the second HRCT (Chi-square test; p=0,63) in all four categories of lung lesions (1. consolidation superimposed on ground-glass opacities (GGOs), 2. crazy paving pattern, including other patterns (e.g., GGOs, consolidation),

Table 2. Results of thoracic CT three months post-discharge compared to initial CT findings.

	Group I (corticosteroid therapy for 14 days)	Group II (corticosteroid therapy for 3 months)	Control group (no additional corticosteroid treatment)	All patients	P*
CT 1 patterns:					
1	16 (53)	24 (55)	9 (47)	49 (53)	0,71
2	7 (23)	13 (30)	4 (21)	24 (26)	
3	7 (23)	6 (14)	5 (26)	18 (19)	
4	0	1 (2)	1 (5)	2 (2)	
Total	30 (100)	44 (100)	19 (100)	93 (100)	
CT 2 patterns:					
1	0	2 (5)	0	2 (3)	0,63
2	1 (5)	0 (0)	0	1 (1)	
3	6 (29)	13 (34)	2 (18)	21 (30)	
4	14 (67)	23 (61)	9 (82)	46 (66)	
Total	21 (100)	38 (100)	11 (100)	70 (100)	

*Chi-square Test. Group I -patients were given corticosteroid treatment for 14 days, group II- patients were given corticosteroid treatment for 3 months, control group did not receive additional corticosteroid treatment. CT patterns: 1. consolidation superimposed on ground-glass opacities (GGO), 2. crazy paving pattern, including other patterns (e.g., GGO, consolidation), 3. GGO predominantly, 4. residual "fibrotic-like" abnormalities. Interpretation of results: rows are showing CT results at baseline (CT 1) and after 3 months (CT 2). For example, from 16 patients in group 1 with CT pattern type 1 at baseline (consolidation superimposed on ground-glass opacities), on follow-up 1 patient changed to CT pattern type 2 (crazy paving pattern, including other patterns), 5 patients changed to CT pattern type 3 (GGOs), and 10 patients to CT pattern type 4 (residual "fibrotic-like" abnormalities).

3. GGOs predominantly, and 4. residual "fibrotic-like" abnormalities) (Table 2), although there was some predominance of reticular fibrotic-like lesions (82%) with less GGOs (18%) in the control group of patients, compared to both glucocorticoid groups. In groups of patients who were taking glucocorticoids were seen GGOs in 29 - 34% of patients, but with less reticular fibrotic-like lesions 66 - 61% of patients. The distribution of patients according to the CT pattern of lung lesions (1.- 4.) and according to the percentage of involvement of the lung parenchyma <5%, 5 - 25%, 25 - 50%, 50 - 75%, and >75%, is on the first CT mostly consolidation superimposed on GGOs affecting from 25 - 75% of lung parenchyma, crazy paving pattern affecting 50 - 75% of lung parenchyma), and GGOs affecting 25 - 50% of lung parenchyma. On the second CT patients had mostly GGO affecting 50 - 75% and >75% of lung parenchyma and residual "fibrotic-like" abnormalities affecting up to 50% of lung parenchyma. There was a significant improvement in CT findings among all three groups in three months follow-up period: for groups I and II (Marginal Homogeneity Test, p< 0,001) and for the control group (p= 0,001). DLCO had been significantly better in the control group compared to the first group 78% (IQR:54 - 81) vrs. 70% (IQR:49,5 - 80,8) and vrs. second group of patients 56% (IQR: 49 - 66,5). The median values of pulmonary function tests are represented in Table 3. There was no statistical difference between group I and II in the patient's symptoms (fatigue, dyspnea, cough, or other). Patients in the control group had significantly fewer dyspnea symptoms (Chi-square test; p=0,04) (Table 3). Laboratory tests analysis after 3 months did not reveal any clinically relevant differences between parameters among all three groups (CRP, NT pro-BNP, ferritin, neutrophils, lymphocytes, thrombocytes, and RDW). No significant complications were observed in patients taking corticosteroid therapy on follow-up examinations. None of the patients died in the follow-up period.

Discussion

This study aimed to investigate lung function, type and extension of lung sequelae on HRCT, and post-COVID-19 symptoms after severe COVID-19 pneumonia in patients who were treated with

Table 3. Lung function and post-COVID-19 symptoms three months after discharge.

	Group I (Corticosteroid therapy for 14 days)	Group II (Corticosteroid therapy for 3 months)	Control group (no additional corticosteroid treatment)	P*
Lung function tests results				
FEV1% (median, IQR)	94 (80,3 - 102)	89,5 (78,8 - 112,3)	92 (84 - 107)	0,82†
FVC% (median, IQR)	91,5 (81 - 105)	91,5 (77 - 107)	98 (82 - 105,5)	0,98†
FEV1/FVC (median, IQR)	80,5 (75,3 - 85)	81 (75,5 - 85)	81 (78 - 84)	0,97†
TLC % (median, IQR)	85 (72,5 - 92)	79 (69 - 90)	89 (77 - 98)	0,29†
DLCO% (median, IQR)	70 (49,5 - 80,8)	56 (49 - 66,5)	78 (54 - 81)	**0,03**†
KCO% (median, IQR)	73,5 (54,3 - 88)	74 (51,3 - 85,5)	78 (28,6 - 82,5)	0,91†
Post COVID-19 symptoms				
Fatigue	13 (43)	18 (41)	6 (32)	0,69
Dyspnea	16 (53)	31 (70)	7 (37)	**0,04**
Cough	7 (23)	8 (18)	1 (5)	0,27
Other	12 (40)	21 (48)	4 (21)	0,14

Abbreviations: *Chi-square test; †Kruskal Wallis test, FEV1 - forced expiratory volume in the first second, FVC - forced vital capacity, TLC - total lung capacity, DLCO - diffusing capacity of the lung for carbon monoxide, KCO - carbon monoxide transfer coefficient.

additional glucocorticoid therapy in two dose regimens with the control group of patients. Patients in all three cohorts were similar by age, gender, smoking status, comorbidities, MEWS score, and prescribed oxygen therapy. Table 2 demonstrates that groups were also similar in CT lung lesion pattern. Due to the lack of knowledge about the optimal therapy regimen, patients received corticosteroid therapy in two different dosing regimens, and some of the patients did not receive additional therapy. The potential bias of the study is that physicians possibly prescribed corticosteroids for patients with more pronounced CT pulmonary changes, however, some of the most severe patients were not candidates for additional corticosteroid therapy because of unregulated diabetes mellitus or unregulated arterial hypertension. Due to the emergency situation during the pandemic and the large influx of patients in COVID-19 center it was only possible to perform initial imaging testing on a 128-slice CT scanner, whereas the second imaging was performed on a HRCT scanner. HRCT was performed for better visualization of post-COVID-19 lung changes. This difference between the two radiological imaging is also a probable cause of the study bias and should be taken into account when interpreting the findings. According to Ray et al. type 2 diabetes mellitus was the most prevalent comorbidity (64,5% of the patients requiring oxygen therapy) in patients with moderate and severe COVID-19 disease who were hospitalized for a prolonged period. Those patients were twice more likely to be males (5). Patients in our study most commonly had arterial hypertension as a comorbidity and median BMI of the patients was 28,8 (25,5 - 31,6). In the study by Hui Chen et al. on 428 critically ill patients with COVID-19 hyperinflammatory phenotype (with elevated levels of proinflammatory cytokines, higher SOFA score, and higher rate of complications) corticosteroids significantly improved survival benefits. Participants were given intravenous corticosteroid therapy for median of 6,5 days (IQR 3 - 11 days). The initial methylprednisolone-equivalent doses were 40 mg, and maximum doses were 40 mg (IQR 40 - 80) (17). Regarding age, gender, and comorbidities such as diabetes mellitus and arterial hypertension patients were similar to the patients in our study, but in that study post-COVID-19 symptoms were not an outcome measure. In the research from Wang et al. on patients with severe COVID-19, the median time from the first symptoms to hospitalization was 8 days. Typical abnormalities on CT were bilateral and multiple consolidations. The median time of hospitalization was 21 days (18). In our study median time

of hospitalization was 26 days (IQR 17,5 - 35,5), and the median time of first symptoms to hospitalization was 9 days (IQR 6 - 12). In severe COVID-19 pneumonia dosing and timing of corticosteroids are unknown (19). Opinions whether corticosteroid therapy should be treatment for the post-COVID-19 lung sequelae are conflicting. There are indications that corticosteroids could be used in disease with persistent lung abnormalities in selected patients to reduce lung sequelae (such as lung fibrosis, etc.) but so far evidence does not support that treatment regimen. Corticosteroids used for COVID-19 pneumonia for up to 10 days are recommended in a selected group of COVID-19 patients in which better survival was reported (12), nevertheless, they are quite commonly used in prolonged regimens in everyday practice in order to potentially reduce lung sequelae and symptoms. They are also used as a prolonged treatment regimen for organizing pneumonia following COVID-19 (20,21). According to study by Chan Sui Ko et al. on 306 hospitalized patients which included 112 patients treated in the intensive care unit, patients given glucocorticoids for a median of 10 days therapy did not improve post-COVID-19 symptoms after 4 months. Regarding age, gender, comorbidities such as arterial hypertension and chronic kidney disease those patients were similar to the patients in our study, but the patients in our study were less likely to have diabetes mellitus (27,5% vrs. 17% patients in our study) and to be current smokers (37% ex-smokers and 5% current smokers vs. 38,2% smokers in the study from Chan Sui Ko). Participants in that study also had 21,9% chronic lung diseases while chronic lung diseases were exclusion criteria in our study (22). According to Mishra et al., the evidence does not support the long-term use of glucocorticoids in COVID-19 to prevent possible sequelae like pulmonary fibrosis (23). Earlier case reports of patients with COVID-19 pneumonia and persistent lung sequelae suggested that patients may have benefit from prolonged steroid treatment (24,25). In an observational study from Myall et al. early treatment of patients with persistent interstitial lung lesions and non-improving symptoms (four weeks post-discharge) with corticosteroids has been associated with significant improvement (19). Diffuse consolidations on chest CT during hospitalization are more common in patients with remaining CT abnormalities than in those with total resolution on control CT. Like previous studies our results suggest consolidations superimposed on GGOs were the most frequent CT findings during hospitalization (18,26). We emphasize that patients in our study had among the most severe radiologic findings in the pandemic wave. In our research 26% of patients had a crazy paving pattern and 53% had consolidations superimposed on GGOs, which corresponds to the research from Pan et al. in which on admission consolidation was present in 59% and "crazy paving" pattern in 25% of patients (26). According to Mylvaganam et al. prolonged course of the disease, days on mechanical ventilation, and immune response with greater levels of cytokines had an impact on the progression of alveolar damage to a fibroproliferative lesions (27). Medications used to treat autoimmune diseases are often used in the severe COVID-19 disease (28). In severe/critical patients, biologics, and immunomodulatory drugs (such as IL-6 receptor antagonists and corticosteroids) against proinflammatory cytokines were used to alleviate the immune response to COVID-19 (28). Understanding the pathogenesis of autoimmune response could assist in preventing the long-term consequences of COVID-19 (8,29-31). It is known that large number of patients who had COVID-19 pneumonia have post-COVID-19 symptoms and persistent pulmonary sequelae. Many of the patients may continue to receive corticosteroid therapy for post-COVID-19 pulmonary sequelae, even though there are not evidence supporting that regimen and patients could only being exposed to side effects of corticosteroid therapy. For patients who have organizing pneumonia as a complication of the disease prolonged corticosteroid therapy is therapy of choice. Macrolide therapy such as clarithromycin had also been successful in the treatment of secondary organizing pneumonia (32). The limitations of this study are the relatively small number of patients, only three months duration of follow-up, and that the patients were not randomized; therefore, it is possible that the physicians were inclined to give corticosteroid therapy to more severe patients. Also, the first CT was performed on a 128-slice CT scanner, whereas the second CT was performed on a HRCT scanner which is also a limitation of this research. Unfortunately, due to the emergency situation during the pandemic and the large influx of patients in COVID-19 center it was only possible to perform such initial imaging testing. Patients with persisting lung infiltrates on control HRCT with reduced lung

function and persistent respiratory symptoms, underwent the pulmonary rehabilitation program and continued further follow-up with a pulmonologist.

Conclusion

Patients who received additional corticosteroid therapy did not have improvement of post-COVID-19 lung abnormalities, post-COVID-19 symptoms, or lung function. The control group of patients had significantly fewer dyspnea symptoms and higher DLCO. So far there is no evidence of the benefit of prolonged corticosteroid therapy for the prevention of post-COVID-19 lung lesions. Immunosuppressive and antifibrotic therapies are being investigated, but so far there are no guidelines for post-COVID-19 interstitial lung disease. According to Schlemmer et al. lung function and pulmonary abnormalities improved up to 1 year after COVID-19 disease, however high percentage of patients with severe disease had significant persistent lung sequelae and post-COVID-19 symptoms that would require prolonged follow-up (33). Randomized controlled trials are needed to institute the rationale for the steroid treatment in specially selected patients who need to be regularly followed due to the risks of side effects. Further studies are needed to understand the pathomechanisms of lung sequelae such as lung fibrosis and to evaluate potential treatment.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author Contributions: ALP, Nevenka PŽ, and AM contributed to writing, analysis, and review. DCK contributed to the design of methodology. NZ, LM, KL, MZ, IK, and DK were involved in data collection, interpretation of data, and critical review.

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