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Steroid pulse -therapy in patients With coronAvirus Pneumonia (COVID-19), sYstemic inFlammation And Risk of vEnous thRombosis and thromboembolism (WAYFARER Study)

Introduction	Coronaviral pneumonia is accompanied not only with severe pulmonary lesions but also with systemic autoimmune inflammation, rapid activation of cytokines and chemokines, i.e., a cytokine storm, as well as a high risk of thrombosis and thromboembolism. Since there is no specific therapy for this new coronavirus infection (COVID-19), an effective and safe anti-inflammatory treatment is needed.
Material and Methods	The efficacy and safety of high-dose pulse glucocorticosteroid (GC) therapy with methylprednisolone 1000 mg for 3 days and dexamethasone 8 mg for another 3–5 days was investigated in 17 patients with severe coronavirus pneumonia using retrospective comparison analysis (control group, n=17). The primary endpoint of the study was the cumulative changes of the patient's condition according to the original SHOKS-COVID score, including changes in the levels of C-reactive protein (CRP) (an inflammation marker), D-dimer (a thrombosis marker), computed tomography (CT) analysis of pulmonary involvement, and, in addition, an assessment of the clinical status. Treated and control patients had signs of pulmonary involvement (53.2% and 25.6%), increases in CRP levels (27- and 19-fold), and more than two-fold increases in D-dimer levels (to 1.41 µg/ml and 1.15 µg/ml). In the GC treatment group, the status of these variables was more severe at baseline.
Results	Pulse GC therapy proved effective and significantly reduced the SHOKS-COVID scores. The median difference was – 5.00 versus the control group (p=0.011). Shortness of breath, oxygen saturation, and the clinical status News-2 score were significantly reduced. In the GC group, CRP levels decreased significantly from 134 mg/dl to 41.8 mg/dl (p=0.009); however, D-dimer levels increased significantly from 1.41 µg/ml to 1.98 µg/ml (p=0.044). Corresponding changes were insignificant in the control group. Changes in the CT findings of pulmonary involvement were more beneficial in the treatment group, but this differences did not reach statistical significance (p=0.062). The high neutrophil counts (p=0.0001) increased even more and, with the persistently low lymphocyte counts, the neutrophil-lymphocyte ratio (NLR), a marker of chronic inflammation, increased 2.5-fold (p=0.006) after the administration of GCs. Changes of the NLR and the D-dimer levels were correlated in the pulse GC therapy group, which emphasizes the association of chronic autoimmune inflammation and thrombosis in COVID-19 (r=0.49, p=0.04). There were no significant changes in the control group. Four patients developed venous thromboembolic complications (pulmonary embolism in two cases) after the pulse GC therapy despite concomitant anticoagulants in therapeutic doses. Recovery in the hormone treatment group was slower, with median duration of hospitalization of 26 days versus 18 days for the control group, p=0.001.
Conclusion	High-dose pulse GC therapy has a rapid anti-inflammatory effect; however, it increases the NLR and the D-dimer levels, which increase the risk of venous thromboembolism.

The new coronavirus disease caused by the SARS-CoV-2 virus, named COVID-19, was confirmed as a pandemic by the World Health Organization (WHO) on 11 March 2020. In severe cases of COVID-19, viral pneumonia develops with severe damage to small lung vessels, bronchioles, and alveoli.

Progressive systemic inflammation accompanied by low lymphocyte and high neutrophil counts plays a significant role in the COVID-19 pathogenesis. Pathological hyper-reactivity of the immune system, which results in uncontrolled activation of immune cells by cytokines in the sites of inflammation, and in the augmented release of cytokines and chemokines by immune cells, is called a cytokine storm. COVID-19 patients demonstrate high levels of interleukins (IL) (IL-1 β, IL-1RA, IL-6, IL-8, IL-9, IL-10, IL-17), macrophage inflammatory protein, vascular endothelial growth factor, tumor necrosis factor-alpha (TNF-α), and other pro-inflammatory chemokines, cytokines, and signaling proteins. The cytokine storm increases the risk of developing acute respiratory distress syndrome and can cause multiple organ failure [1].

Glucocorticosteroids (GCs) are one of the most common anti-inflammatory agents with a long history of use. Currently, the WHO does not recommend routine use of corticosteroids in patients with viral pneumonia or acute respiratory distress syndrome, unless the patients have other conditions, such as asthma, acute exacerbation of chronic obstructive pulmonary disease, or septic shock [2]. The Interim Guidelines of the Ministry of Health of the Russian Federation mention the possibility of using GCs in low doses (methylprednisolone 1 mg/kg/day, intravenously) as a preventive anti-inflammatory therapy. However, pulse GC therapy is not included in the list of tactics for treatment of COVID-19 recommended by the Ministry of Health in the Interim Guidelines for the Prevention, Diagnosis, and Treatment of New Coronavirus Disease (COVID-19), 7th revision [3].

However, GCs, due to their high availability, are often used in the treatment of the inflammation and cytokine storm caused by the SARS-CoV-2 virus. A systematic review of 41 studies of 25 protocols for treatment of COVID-19 found that corticosteroid therapy was commonly used in different doses and regimens [4]. Unfortunately, GCs have many side effects. Some of the major medium-and long-term adverse effects of this group of agents are increased insulin resistance [5–7], increased cardiovascular risk, and risk of bacterial infections [8]. Glucose metabolism disorders and increased risk of superinfections can be corrected in the setting of inpatient treatment of coronavirus pneumonia. The most dangerous side effect is an increased risk of thrombotic and thromboembolic complications, which are already characteristic of COVID-19, and which may cause multiple organ failure and worsen the prognosis. Several studies have shown that COVID-19 can be accompanied by hypercoagulation with inhibition of fibrinolysis. This leads to microthrombosis in the lung, kidney, and heart vessels, and an increased risk of venous thromboembolism (VTE), including pulmonary embolism (PE), arterial thromboembolism, and stroke [9, 10]. Moreover, an increased level of D-dimer, a fibrin degradation product used as a marker of increased risk of thrombosis, is an independent factor determining the poor prognosis of patients with COVID-19 [10, 11]. Anticoagulant therapy becomes more common as knowledge accumulates and as understanding of the pathogenesis of the coronavirus disease improves [11]. GC treatment may potentially reduce the efficacy of preventive treatment with low-molecular-weight heparin (LMWH) due to an increased risk of thrombosis.

The study of the efficacy i.e., possible suppression of inflammation and cytokine storm and the safety, i.e., possible progression of cardiovascular complications and thrombosis, of glucocorticoid therapy in patients with COVID-19 is of scientific interest and practical significance.

We performed a retrospective cohort comparative study of 34 patients with severe coronavirus pneumonia who required anti-inflammatory treatment. The objective of the study was to evaluate the clinical efficacy and safety of high-dose pulse GC therapy (a three-day course with a one-week maintenance) in patients with COVID-19.

Material and methods

The study included 34 patients with a proven diagnosis of coronavirus pneumonia who were admitted to the Medical Research and Educational Center of Lomonosov Moscow State University (Lomonosov University Clinic). In all the cases, the diagnosis was confirmed by determining the presence of SARS-CoV-2 virus RNA with polymerase chain reaction and typical computed tomography (CT) findings in the lung tissue. Initially, standard treatment with hydroxychloroquine and azithromycin was administered, with bromhexine and spironolactone added later. Moreover, all patients were treated with the anticoagulant LMWH, with the dose of LMWH calculated according to body weight. The patients were treated with LMWH from the first day of hospitalization and, in case of an increase in the levels of D-dimer ≥5 µg/ml, they were given therapeutic doses. If necessary, antibacterial therapy was adjusted. Patients in both groups took a mean of 1.4 antibiotic agents.

There were no differences in both auxiliary therapy and in ordering agents for the treatment of comorbidities between the groups. Patients who required emergency anti-inflammatory therapy due to high fever, low blood oxygen saturation, elevated C-reactive protein (CRP), and the absence of changes in the CT scans were included in the GC treatment group (n=17). In the absence of anti-interleukin agents, it was decided to perform pulse treatment with high doses GCs: methylprednisolone 1000 mg intravenously for 3 days with subsequent dexamethasone 4 mg twice a day for 3–7 days. One patient additionally received tocilizumab 400 mg. Five patients received colchicine 0.5 mg/day after the end of corticosteroid therapy. The control group comprised 17 patients with similar basic characteristics who were also treated in the Lomonosov University Clinic using the same protocols, but who did not receive pulse GC therapy. One patient received tocilizumab 400 mg. Only six of them were treated with colchicine 1 mg on the first day and 0.5 mg/day afterward. No other specific anti-inflammatory therapy was performed in either group. The duration of observation was 10 days for both groups: 10 days from the start of treatment in the GC treatment group, and 10 days from the time of inclusion in the control group. Analysis of data from the GC treatment and control groups was performed using double-blind endpoints for data sampling and statistical processing stages, which eliminated influence of the subjective factor on the findings.

The baseline characteristics of patients are given in Table 1. In the pulse GC therapy group, the median age was 59 years, and 15 of the 17 (88.2%) patients were male with a median body mass index of 29.9 kg/m². In the control group, the median age was higher, 68 years. This group included more male patients (58.5%) with a mean body mass index of 27.8 kg/m², but no differences were statistically significant. The groups did not differ in the number and prevalence of concomitant diseases, including cardiovascular disease with predominant hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and cancer.

In the pulse GC therapy group, patients had significantly more severe fever than those in the control group (median difference was 0.9°C), more severe, but not statistically significant, severe shortness of breath (median respiratory rate (RR) 24 vs. 19 breaths per minute), which was associated with lower oxygen saturation (median levels 85% vs. 94% in room air and 92% vs. 96% with oxygen therapy). All patients in the GC treatment group received oxygen therapy versus 53% in the control group (p=0.002). They were more

likely to have been transferred to the intensive care unit (ICU) and to have received assisted ventilation (AV), although there were no significant differences in these parameters between the groups. The groups did not differ significantly in baseline systolic blood pressure (SBP). Tachycardia was observed in the group of more severely ill patients who received pulse GC therapy.

Both groups had characteristics of severe coronavirus pneumonia and did not differ in most parameters of the biochemical profile. The cumulative indicator of inflammation severity (C-reactive protein [CRP]) was 19-time higher than normal in the control group and 27-times higher than normal in the GC treatment group (p=0.048). The levels of D-dimer were increased three-fold in the GC treatment group compared to the control group, which reflected an increased tendency for thrombosis during the inflammatory process along with elevated levels of fibrinogen (p=0.125). Both groups demonstrated low lymphocyte and high neutrophil counts which exceeded normal values only in the GC treatment group. The neutrophil-lymphocyte ratio (NLR) was 4.06 in the control group and 6.05 in the GC treatment group (p=0.125). Platelet count, glucose, creatinine, and estimated glomerular filtration rate (GFR) were within normal limits and did not differ between the groups.

Lung and chest computed tomography (CT) scans were produced using a 32 slice SOMATOM Scope CT scanner (Siemens, Germany). The scans were obtained with 1-mm slices. During the first examination, the standard CT protocol (tube voltage 120 kV, automatic tube current modulation 200–400 mA) was used. The following investigations were carried out using a low-dose CT protocol with reduced tube voltage (100 or 110 kV) and automatic tube current modulation (40–120 mA). The mean radiation exposure was 3.9±0.4 mSv under the standard protocol and 0.9±0.2 mSv under the low-dose protocol. CT scans were performed at admission and discharge and were repeated during hospitalization as deemed clinically necessary, but at least once every 5 days. All the scans were stored in DICOM format in the radiological information network (PACS/RIS) of the Medical Research and Educational Center of Lomonosov Moscow State University. The CT scans were processed and analyzed in Syngo.via (Siemens) workstations. A semi-quantitative score for assessing the amount of infiltration and consolidation areas of the lung tissue was used to process and interpret CT findings, as recommended by the Interim Guidelines of the Russian Ministry of Health «Prevention, Diagnosis and Treatment of New Coronavirus Disease (COVID-19) 6 and 7 versions (CT1–CT4).

Table 1. Baseline patient characteristics

Parameters	Pulse GC therapy group*, n=17	Control group, n=17	p	n
General characteristics				
Age, years, median [25%; 75%]	59.0 [52.0; 67.0]	68.0 [46.0; 81.0]	0.309	34
Male, n (%)	15 (88.2%)	10 (58.8%)	0.125	34
Hypertension, n (%)	12 (70.6%)	9 (52.9%)	0.480	34
BMI, kg/m², median [25%; 75%]	29.9 [27.0; 32.4]	27.8 [27.0; 31.8]	0.607	31
CAD, n (%)	2 (11.8%)	2 (11.8%)	1.000	34
Diabetes mellitus, n (%)	2 (11.8%)	1 (5.88%)	1.000	34
COPD, bronchial asthma, n (%)	1 (5.88%)	2 (11.8%)	1.000	34
Cancers, n (%)	1 (5.88%)	1 (5.88%)	1.000	34
Clinical characteristics				
Body temperature, °C, median [25%; 75%]	37.8 [37.2; 38.1]	36.9 [36.6; 37.1]	0.006	34
RR, breaths per min, median [25%; 75%]	24.0 [19.0; 26.0]	19.0 [18.0; 22.0]	0.069	34
HR, bpm, median [25%; 75%]	97.0 [82.0; 104]	78.0 [70.0; 88.0]	0.016	34
SBP, mm Hg, median [25%; 75%]	123 [120; 130]	120 [115; 130]	0.690	34
SpO$_2$ room air, %, median [25%; 75%]	85.0 [80.0; 89.0]	94.0 [93.5; 96.0]	<0.001	32
SpO$_2$ oxygen support,%, median [25%; 75%]	92.0 [90.0; 93.0]	96.0 [96.0; 98.0]	0.006	26
Any oxygen support, n (%)	17 (100%)	9 (52.9%)	0.002	34
ICU, n (%)	12 (70.6%)	6 (35.3%)	0.084	34
AV, n (%)	6 (35.3%)	1 (5.88%)	0.085	34
Biochemical characteristics				
CRP, mg/dL	134 [112; 194]	95.1 [67.0; 134]	0.048	34
D-dimer, µg/ml	1.41 [1.20; 1.96]	1.15 [1.00; 1.36]	0.125	34
Fibrinogen, g/l	6.83 [5.84; 7.32]	5.93 [5.48; 7.29]	0.318	32
Lymphocytes, 109/l	0.66 [0.48; 1.29]	1.05 [0.89; 1.14]	0.221	34
Neutrophils, 109/l	5.02 [3.06; 6.38]	4.23 [3.00; 6.33]	0.617	34
Neutrophil/lymphocyte ratio	6.05 [3.80; 11.2]	4.06 [2.12; 5.45]	0.125	34
Platelets, 109/l	216 [179; 248]	196 [158; 264]	0.642	34
Glucose, mmol/l	6.06 [5.10; 7.60]	6.05 [5.78; 6.49]	0.547	34
Creatinine, µmol/l	91.0 [86.0; 102]	82.0 [64.0; 105]	0.438	34
GFR, ml/min/1.73 m² (CKD-EPI)	78.0 [63.0; 87.0]	76.0 [65.0; 98.0]	0.783	34
Lung lesion*				
CT stage	3.00 [2.00; 3.00]	2.00 [1.00; 2.00]	<0.001	34
CT 3–4, n (%)	10 (58.8%)	0 (0.00%)	<0.001	34
CT lesion (%)	53.2 [37.3; 65.1]	25.6 [12.6; 34.7]	<0.001	33
Cumulative risk				
NEWS-2 score	11.0 [6.00; 12.0]	5.00 [4.00; 5.50]	<0.001	32
SHOKS-COVID score	13.0 [11.0; 15.0]	7.00 [6.00; 9.00]	<0.001	34

*, before the start of pulse therapy. **, the median stage of cumulative pulmonary involvement according to the CT findings under the Guidelines of the Russian Ministry of Health and the Moscow Health Department. CRP, C-reactive protein; GFR, glomerular filtration rate; CT, computed tomography. The quantitative data are expressed as the median and interquartile range.

The Russian software complex Gamma Multivox was used for an accurate quantitative analysis of the changes in the volume of alterations of the lung parenchyma caused by COVID-19 in all cases, with a special application for analyzing COVID-19 lung tissue lesions. This software was created by the laboratory of medical computer systems of D. V. Skobeltsyn Moscow State University and the Faculty of Fundamental Medicine (FFM) of the Lomonosov Moscow State University (https://multivox.ru), and was used for the analysis of all the CT scans of each subject. This included automatic color-coding and calculation of the amount of ground-glass opacities and consolidations on CT images, estimation of the volume in cubic centimeters and as a percentage relative to the lung volume. The sum of any ground-glass opacities and consolidation areas was taken into account. The program generated a table with measured values, and new data was added to the table as examinations were performed. Laboratory tests included 1) blood biochemical profile (CRP, creatinine, urea, glucose)

performed on an automatic biochemical analyzer AU480 Beckman Coulter, Germany, 2) complete blood count (5 diff) performed on a hematological analyzer XN 2000 Sysmex Corporation, Japan, 3) hemostasis analysis (fibrinogen, D-dimer) performed on an automatic hemostasis analyzer STA-Compact Diagnostics Stago SAS, France.

According to the CT findings, all 34 patients had signs of bilateral viral pneumonia typical for COVID-19 disease. According to the classification recommended by the Russian Ministry of Health and the Moscow Health Department [3], the median of stages was 2.0 in the control group and 3.0 in the GC treatment group. In the GC treatment group, 58.8% of patients had stage 3–4 pulmonary involvement, but there were no such patients in the control group. The computer analysis (MultiVox, FFM MSU) found that the cumulative volume of pulmonary involvement (ground-glass opacity, crazy-paving pattern, areas of consolidation and fibrosis) was 25.6% in the control group and 53.2% in the GC treatment group (p<0.001).

We used two scores to objectify the severity of the clinical condition and to adequately assess the effects of the therapy:
1) the NEWS-2 score (National Early Warning Score (NEWS) 2, Standardizing the assessment of acute-illness severity in the NHS. Updated report of a working party. London: RCP, 2017), modified for patients with COVID-19 [12],
2) the SHOKS-COVID score, our original clinical assessment scale for patients with coronavirus disease.

The NEWS-2 score was designed to assess the severity of the condition of patients with acute respiratory syndromes. It has been widely used for many years to evaluate the risk of clinical deterioration, for timely and competent decision-making on the manner of treatment, and for the need for treatment intensification. This score has been validated in several populations, and it has been used for rapidly assessing the risk of clinical deterioration and for triage of patients with COVID-19. It is based on common clinical manifestations: RR, oxygen saturation, the need for assisted ventilation, state of consciousness, body temperature, as well as heart rate (HR) and SBP. However, it does not sufficiently take into account the characteristics of patients with COVID-19. Chinese researchers supplemented this score with an age parameter and added the maximum number of points (3) for age of over 65 years [12]. That modification reflected an early understanding of the course of COVID-19 during the outbreak in Wuhan. It is evident now that age is not the only aggravating factor. Concomitant diseases also worsen the prognosis. The maximum risk of death

is observed in the subgroup of patients over 80 years old, in which this risk is 6 times higher than in patients aged 65 [13]. According to the modified NEWS-2 score, low risk of poor prognosis is indicated by score 0, mild risk by 1–4, high risk by 5–6, and very high risk by 7 or more. The median NEWS-2 score in patients of the control group was 5, corresponding to high risk, and in patients of the GC treatment group, this score was 11, corresponding to very high risk.

Assessment of the condition of patients with COVID-19 depends on several key parameters, not only the severity of shortness of breath, oxygen saturation, and the need for lung ventilation. These parameters further characterize the severity of pulmonary involvement and respiratory failure. The state of consciousness is directly correlated with the patient's admission to the ICU and predominantly with receiving AV. The amount of damage to the lung tissue according to the CT findings is one of the key parameters, which is not always correlated with clinical manifestations of shortness of breath, as well as the severity of the inflammatory process, the main markers of which are the severity of fever and the level of CRP. Moreover, the risk of thrombotic and thromboembolic complications that accompany damage of the lung tissue, which is determined by the level of the D-dimer, can be used as one of the main prognostic factors indicating an adverse course of the disease.

Based on the successful experience of developing an integral clinical assessment score (SHOKS) for patients with chronic heart failure (Yu. N. Belenkov and V. Yu. Mareev, 2000), we developed our original score to determine the clinical status of patients with COVID-19 by taking into account the main markers of the disease severity, (SHOKS – COVID, see Table 2). The score 0 to 3 corresponds to low risk, 4–6 to medium risk, 7–10 to serious risk (i.e., above average), 11–14 to high risk, and finally, the score of 15 or higher to extremely high risk of an unfavorable course of the disease, with rapid progression of pulmonary involvement, multiple organ failure, conditions which are extremely difficult to treat. This score was based on theoretical assumptions but not on data from any cohort analysis nor the definition of risk groups and has not yet been validated.

The median SHOKS-COVID score was 7.0 for patients of the control group, which corresponds to above-mean risk, and 12.0 for patients who received pulse GC therapy, which indicates high risk. As we can see, the condition of patients in both groups was rated as much more severe according to the NEWS-2 score than by the SHOKS-COVID score. However, distinguishing between the high and very high risk is always mostly a philosophical question.

The decision to conduct more active anti-inflammatory treatment with GCs in the GC treatment group was mainly determined by the identified differences in the clinical course of the disease. The primary endpoint of the study was the change in the SHOKS-COVID score. The secondary endpoints were the changes in the clinical score (NEWS-2) and oxygen saturation (SpO_2), changes in the blood levels of CRP and D-dimer, and estimation of the degree of pulmonary involvement on CT scans in Multivox.

Statistical Analysis

Quantitative data are expressed as the median and interquartile range (Me and 25%;75%), whereas qualitative data are presented as absolute and relative values. The significance of intergroup differences in qualitative characteristics was assessed using the χ^2 test and two-way Fischer's exact test. The quantitative data were compared between groups using the Mann-Whitney U-test. To compare intragroup changes of parameters, the Wilcoxon signed-rank test was used for related samples with quantitative data, and McNemar's test was used for qualitative data.

A logarithmic data transformation was performed, followed by the calculation of the Pearson correlation coefficient to assess correlations of parameters with nonparametric distributions. The threshold for statistical significance was $p<0.05$. Statistical analyses were performed using the R programming language in the R Studio.

Results

The changes in the SHOKS-COVID scores as the primary endpoint are shown in Figure 1. The median SHOKS-COVID score increased insignificantly from 7.00 [6.00; 9.00] to 9.00 [5.50; 10.0] (p=0.148) in the control group and remained in the same risk category, i.e., above average. It decreased from 13.0 [11.0; 15.0] to 10.0 [7.0; 13.0] (p=0.01) in the pulse GC therapy group. After treatment values differed significantly, +1.00 [−2.25; +3.00] in the control group and − 4.00 [−5.00; −2.00;] in the pulse GC therapy group (p=0.011).

Figure 2 shows the changes in the clinical condition as measured by the NEWS-2 score. In the control group, the score decreased insignificantly from 5.00 [4.00; 5.50] to 3.00 [3.00; 6.50] (p=0.97). In the GC treatment group, this decrease from 11.0 [6.00; 12.0] to 6.00 [3.75; 9.25] was significant (p=0.026). Both groups also significantly differed in the amount of decrease as measured by the NEWS-2 clinical score: −1.00 [−2.00; +2.50] vs. −3.50 [−4.50; −0.75]

Table 2. Clinical Assessment Score for Patients with COVID-19 (SHOKS-COVID) based on Mareev modification 2020

| Parameter	Value	Score
1) RR at rest	<18	0
	18–22	1
	23–26	2
	>26 (or AV)	3
2) Body temperature	35.5–37°C	0
	37.1–38.5°C	1
	>38.5°C	2
3) SpO_2	>93%	0
	90–92.9%	1
	<90%	2
4) Ventilation	Not needed	0
	Low-flow ventilation in room air	1
	Non-invasive lung ventilation in the ICU	2
	Invasive assisted ventilation in the ICU	3
5) CRB, mg/dl	<10	0
	10–60	1
	60–120	2
	>120	3
6) D-dimer, µg/ml	<0.5	0
	0.51–2.00	1
	2.01–5.00	2
	>5.00	3
7) CT lung lesion based on computer analysis (%)	No pneumonia	0
	0–24%	1
	25–49%	2
	50–74%	3
	75–100%	4
TOTAL	MAXIMUM	20

RR, respiratory rate; SpO2, oxygen saturation; CRP, C-reactive protein; GFR, glomerular filtration rate; CT, computed tomography; AV, assisted ventilation; ICU, intensive care unit

in the control and pulse GC therapy groups, respectively (p=0.043).

The maximum difference in the change of the patients' well-being was due to changes in oxygen saturation and reduced shortness of breath (Figure 3). This parameter did not change in the control group: 94.0 [93.5; 96.0] % at baseline and 94.0 [89.5; 97.0] % after treatment (p=0.51). Oxygen saturation increased significantly in the pulse therapy group from 85.0 [80.0; 89.0] % to 93.0 [91.5; 95.0] % (p=0.025). In the GC treatment group, the changes of this parameters were clearly more significant: +8.00 [+2.25; +13.0] % vs. +1.00 [−6.00; +4.00] % in the control group (p=0.008).

Other changes in clinical parameters are provided in Table 3. As shown in the table, patients in the pulse GC

Figure 1. Cumulative changes of the condition and prognosis in patients with COVID-19 (SHOKS-COVID) during the treatment
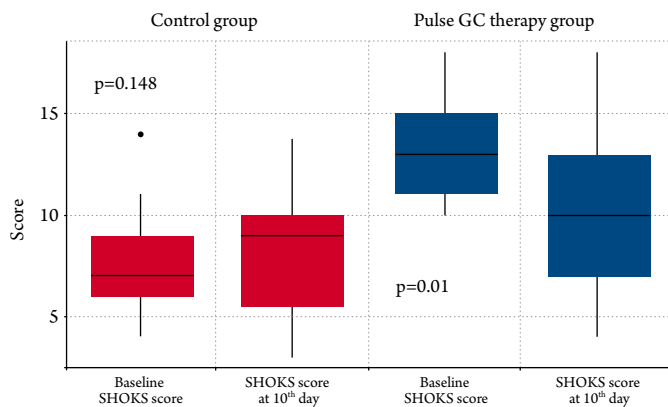
The median is the horizontal line inside the rectangular boxes; the upper border of a rectangular box is the 75th percentile, the lower border is the 25th percentile. The black lines show values that are within the 1.5 inter-quartile range from the 25th and 75th percentiles. Individual points show the values lying outside the borders.

Figure 2. Cumulative changes in the clinical status of patients with COVID-19 (NEWS-2 score, COVID-19 modification) during the treatment
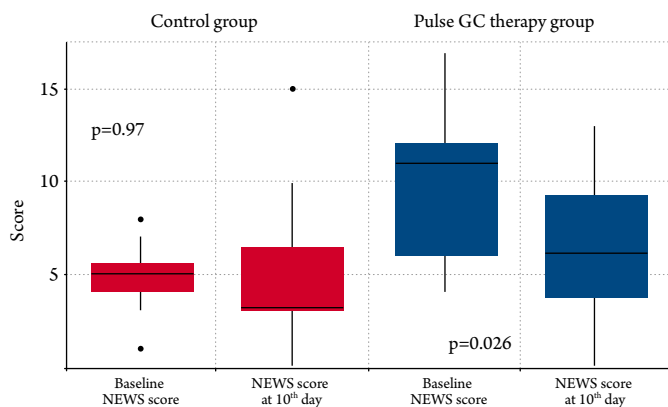
The median is the horizontal line inside the rectangular boxes; the upper border of a rectangular box is the 75th percentile, the lower border is the 25th percentile. The black lines show values that are within the 1.5 inter-quartile range from the 25th and 75th percentiles. Individual points show the values lying outside the borders.

therapy group had a statistically significant decrease in body temperature to normal values, reductions of RR by 5 breaths per minute and in heart rate by 13 bpm. The number of patients in the ICU decreased from 12 to 8; one of them was transferred from AV to non-invasive lung ventilation, and the number of patients in clear consciousness increased from 8 to 11. No significant changes occurred in the control group, which once again characterizes coronavirus pneumonia as a very persistent disease that is barely treatable at the stage of an extensive inflammatory process in the lung tissue.

Figure 4 shows the results of computer processing of the chest CT scans with determination of the cumulative percentage of pulmonary involvement at the time of inclusion and on Day 10 of observation. The sum of any ground-glass opacities and consolidation areas was taken into account. Despite the treatment, the cumulative volume of pulmonary involvement unexpectedly increased significantly from 25.6 [12.6; 34.7] % to 44.9 [23.3; 52.2] % (p=0.0026) in the control group. Taking into account the absence of changes in oxygen saturation and shortness of breath, it is possible that, with a higher degree of involvement, non-ventilated areas of the lungs (consolidations) could turn into partially ventilated areas (ground-glass opacities). The stage analysis, according to the Guidelines of the Russian Ministry of Health, showed no clinical meaningful changes in the data: the median was 2.00 [1.00; 2.00] at baseline and 2.00 [2.00; 3.00] at the end of the observation, although this difference was statistically significant (p=0.0147). The degree of pulmonary involvement according to the computer analysis did not change in the GC treatment group: 53.2 [37.3; 65.1] % at baseline and 53.9 [41.3; 68.4] % after the GC treatment (p=0.67). The stage of pulmonary

Table 3. Changes in the clinical status of patients before and after treatment

Parameters	Hormone therapy (n = 17)		p	Control group (n = 17)		p
	Baseline	In 10 days		Baseline	In 10 days	
Body temperature, ^{0}C	37.8 [37.2; 38.1]	36.6 [36.2; 37.0]	0.004	36.9 [36.6; 37.1]	36.6 [36.3; 36.9]	0.109
RR, breaths per min	24.0 [19.0; 26.0]	19.0 [16.0; 22.0]	0.117	19.0 [18.0; 22.0]	19.0 [18.0; 20.0]	0.291
HR, bpm	97.0 [82.0; 104]	84.0 [76.0; 88.0]	0.092	78.0 [70.0; 88.0]	80.0 [73.0; 86.0]	0.343
SBP, mm Hg	123 [120; 130]	120 [115; 130]	0.67	120 [115; 130]	118 [110; 122]	0.075
SpO$_2$, room air, %	85.0 [80.0; 89.0]	93.0 [91.5; 95.0]	0.025	94.0 [93.5; 96.0]	94.0 [89.5; 97.0]	0.512
SpO$_2$, vent., %	92.0 [90.0; 93.0]	96.0 [91.8; 98.0]	0.261	96.0 [96.0; 98.0]	96.0 [92.5; 97.5]	0.752
Any O$_2$ support, n (%)	17 (100%)	13 (76.5%)	0.133	9 (52.9%)	11 (64.7%)	0.683
ICU, n (%)	12 (70.6%)	8 (47.1%)	0.288	6 (35.3%)	4 (23.5%)	0.683
AV, n (%)	6 (35.3%)	5 (29.4%)	0.133	1 (5.88%)	2 (11.8%)	1
Alteration of consciousness, n (%)	9 (52.9%)	6 (35.3%)	0.371	0 (0.00%)	3 (17.6%)	0.248

RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; SpO₂, oxygen saturation; ICU, intensive care unit; AV, assisted ventilation. The quantitative data are expressed as the median and interquartile range.

Figure 3. Changes in oxygen saturation in room air (without oxygen support) in patients with COVID-19 during the treatment
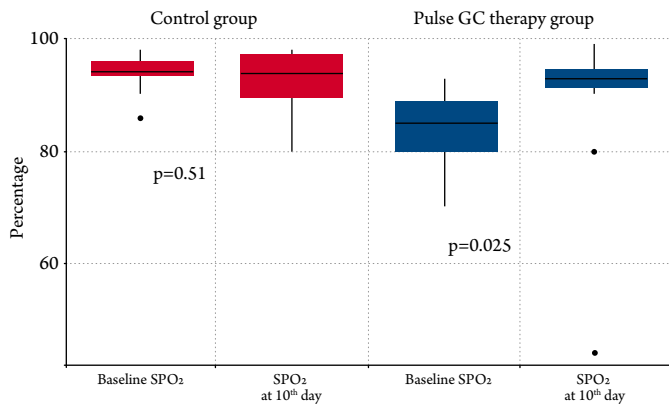
The median is the horizontal line inside the rectangular boxes; the upper border of a rectangular box is the 75th percentile, the lower border is the 25th percentile. The black lines show values that are within the 1.5 inter-quartile range from the 25th and 75th percentiles. Individual points show the values lying outside the borders.

Figure 4. Changes in the percentage of pulmonary involvement in CT patients with COVID-19 during the treatment
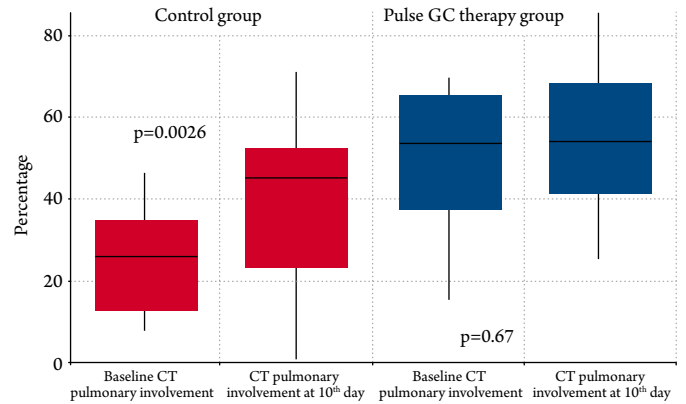
The median is the horizontal line inside the rectangular boxes; the upper border of a rectangular box is the 75th percentile, the lower border is the 25th percentile. The black lines show values that are within the 1.5 inter-quartile range from the 25th and 75th percentiles. Individual points show the values lying outside the borders.

involvement also did not change: median values were 3.00 [2.00; 3.00] before and after pulse GC therapy (p=0.82). We can also assume that a significant decrease in shortness of breath, an increase in oxygen saturation, and lower rates of oxygen support were associated more with qualitative, 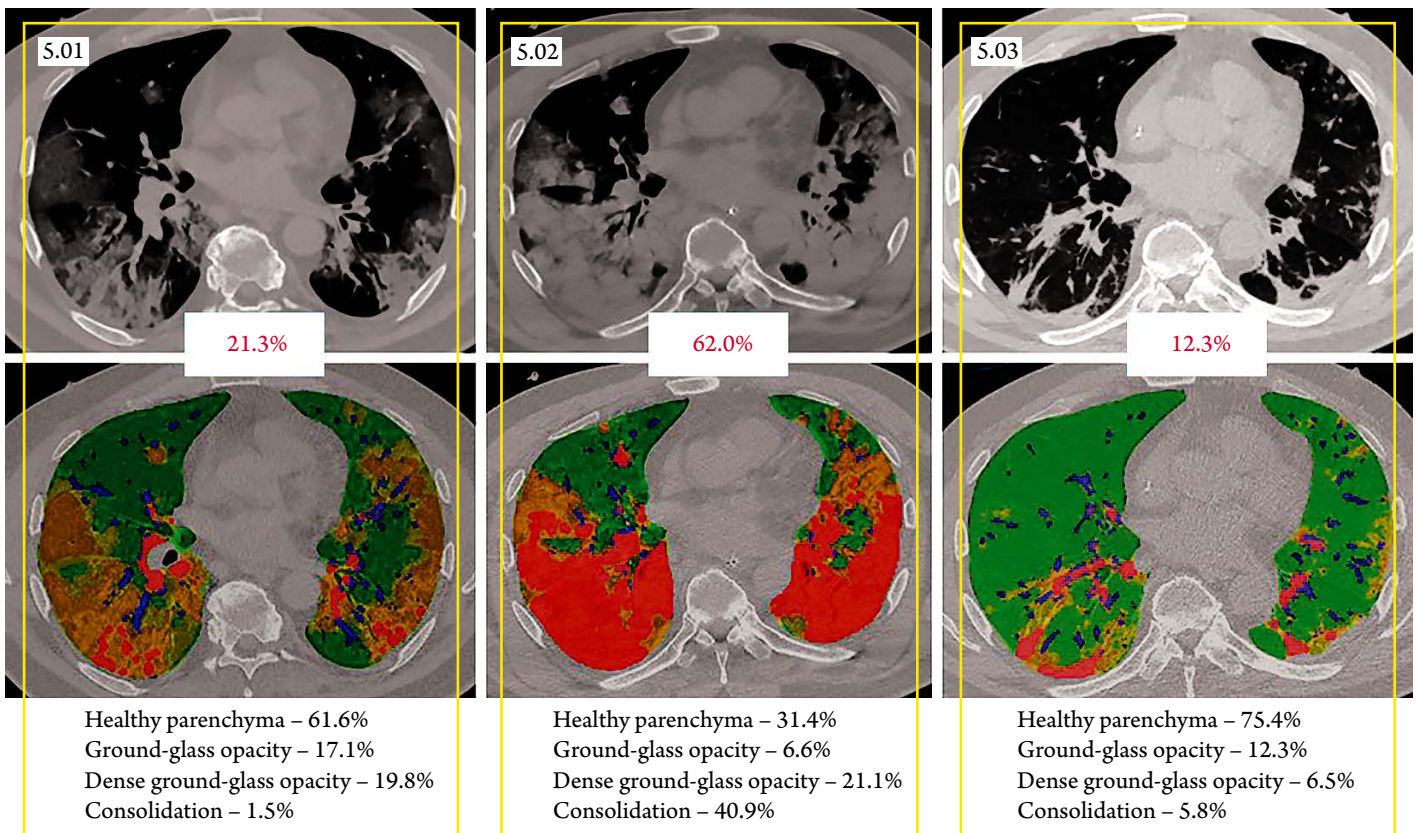rather than quantitative, characteristics of pulmonary involvement. Anyway, the median change in the degree of pulmonary involvement according to CT findings was only + 0.75 [–10.95; +13.9] % in the pulse GC therapy group and +17.6 [+0.10; +23.6] % in the control group; these differences did not reach statistical significance (p=0.062).

Figure 5. Computer quantitative processing of CT lung findings, patient I., 44 years old; explanations are given in the text. Figures 5.01: 22.04.2020; 5.02: 29.04.2020; 5.03: 10.05.2020

Healthy parenchyma – 61.6%
Ground-glass opacity – 17.1%
Dense ground-glass opacity – 19.8%
Consolidation – 1.5%

Healthy parenchyma – 31.4%
Ground-glass opacity – 6.6%
Dense ground-glass opacity – 21.1%
Consolidation – 40.9%

Healthy parenchyma – 75.4%
Ground-glass opacity – 12.3%
Dense ground-glass opacity – 6.5%
Consolidation – 5.8%

The percentage of severe pulmonary involvement (dense ground-glass opacities and consolidations) is given within the rectangular box

We present a case report (Figure 5) of a 44-year-old patient I, who was admitted to the Lomonosov University Clinic on 22 April 2020 (Day 2 of admitting patients with COVID-19), with moderate pulmonary involvement of 38.4%, of which the minimum severity in the form of ground-glass opacities (light yellow) was 17.1%, high severity in the dense ground-glass opacities (brown) was 21.3%, and consolidations (red) was 1.5%.

The patient had had low-grade fever for three days (37.6°C), no severe shortness of breath (RR 18 breaths per min), respiratory oxygen saturation 94%, CRP 38.6 mg/dL, D-dimer 0.89 µg/ml during administration of imidazolyl ethanamide pentandioic acid, hydroxychloroquine, and azithromycin which were prescribed before admission to the hospital. The patient's status was reasonably good. Azithromycin was continued. Bromhexine was administered 8 mg x 4 times a day instead of hydroxychloroquine, spironolactone 50 mg x 2 times a day, and enoxaparin sodium 40 mg x 2 times a day. Similar therapy was used in the control group.

Until 28 April 2020, the patient's status gradually worsened, antibiotic therapy was changed, and the dose of enoxaparin sodium was increased to 80 mg x 2 times a day. But on 29 April 2020, the condition deteriorated critically. Figure 5.02 shows the CT findings as of 29 April 2020. Pulmonary involvement increased to 68.6% with only 6.6% of ground-glass opacity, 21.1% of dense ground-glass opacity, and 40.9% of consolidation (severe lesion 62%). The patient had a fever of 38.5 C, RR 26 breaths per min, HR 120 bpm, oxygen saturation 78%, CRP 425 mg/dL, D-dimer 1.33 µg/ml. Neutrophil counts were increased to 7.55x10^9/l, and lymphocyte counts were decreased to 0.47x10^9/l. The neutrophil-lymphocyte ratio (NLR) was 16.06. The patient was transferred to the ICU and put on AV. Given the severity of the disease, acute inflammation, and the absence of agents acting on interleukins, it was decided to perform pulse treatment with methylprednisolone 1000 mg for 3 days, followed by dexamethasone 8 mg x 2 times a day for 5 more days. Then, the patient received colchicine 1 mg on the first day and 0.5 mg on the following days before discharge. As a result, CRP levels decreased 4-fold, fibrinogen levels from 11.07 to 7.2 g/l, SpO$_2$ from 78% to 94%, RR decreased to 20 breath per min, and HR to 92 bpm. The D-dimer increased insignificantly to 1.63 mg/ml. Neutrophil counts increased to 17.2x10^9/l, and lymphocyte counts increased to 1.39x10^9/l. The NLR decreased to 12.4. The degree of pulmonary involvement significantly decreased by Day 10 after the start of pulse GC therapy (Figure 5.03)

with an evident anti-inflammatory effect. Ground-glass opacity was moderate and consolidation lesions of the lung tissue was 12.3%. The cumulative volume of the unaffected lung tissue increased to 75.4%. The patient was extubated on Day 6 after the pulse GC therapy, transferred from the ICU on Day 10, and discharged from the hospital on Day 14 with recommendations to take colchicine 0.5 mg/day and rivaroxaban 10 mg/day. The follow-up examination is scheduled on day 45.

Table 4 shows changes in the laboratory parameters in the GC treatment and control groups. Changes in the CRP levels, as the most common marker of the severity of the inflammatory process, were of the greatest interest. It decreased statistically significantly in the GC treatment group (p=0.009) and insignificantly in the control group. The median decrease was twice as large in the GC treatment group (−85.57 [−155.3; −2.36] mg/dL) than in the control group (+41.03 [−65.0; +24.3] mg/dL), but the differences were not significant (p=0.109). However, the baseline levels of CRP were higher by 39 mg/dl in the GC treatment group, and after the treatment, on the contrary, the levels were higher in the control group by 15 mg/dl. The CRP levels decreased significantly (by more than 10%) in 13 (76.5%) patients in the GC treatment group and in 6 (35.3%) patients in the control group.

D-dimer levels increased significantly in the GC treatment group (p=0.044), but they did not change in the control group (p=0.31). The median increase was + 0.66 [−0.11; +9.16] µg/ml (47% of the baseline value) in the GC treatment group and +0.01 [−0.64; +0.47] µg/ml in the control group (p=0.040). An increase in the D-dimer levels by more than 10% was observed in 12 (70.6%) patients in the GC treatment group. Two patients experienced PE, and two more patients developed venous thrombosis of the extremities (4/17=23.5%). In these cases, the D-dimer levels increased to 12.8 and 20.0 µg/ml in PE and to 13.5 and 12.5 µg/ml in venous thrombosis, respectively. In the control group, no significant increases in the D-dimer levels and thrombotic complications were detected. Changes in fibrinogen levels were minimal in both groups.

A baseline decrease in lymphocyte counts was observed in both groups, mostly among patients who were treated with GCs. They did not significantly change by the end of observation in either group. Neutrophil counts barely changed and even tended to decrease in the control group. As is typical with GC treatment, neutrophil counts significantly increased by 73% (p<0.0001)

Table 4. Changes in laboratory values in patients before and after treatment

Parameters	Hormone therapy (n=17)		p	Control group (n=17)		p
	Baseline	Changes		Baseline	Changes	
CRP, mg/dL	134 [112; 194]	41.8 [22.6; 101]	0.009	95.1 [67.0; 134]	56.9 [9.48; 122]	0.306
D-dimer, µg/ml	1.41 [1.20; 1.96]	1.98 [1.63; 10.0]	0.044	1.15 [1.00; 1.36]	1.21 [0.73; 1.94]	0.860
Fibrinogen, g/l	6.83 [5.84; 7.32]	6.72 [4.82; 7.55]	0.322	5.93 [5.48; 7.29]	6.50 [6.25; 6.99]	0.742
Lymphocytes, 10^9/l	0.66 [0.48; 1.29]	0.70 [0.51; 0.95]	0.943	1.05 [0.89; 1.14]	1.24 [0.69; 1.63]	0.306
Neutrophils, 10^9/l	5.02 [3.06; 6.38]	8.68 [6.77; 14.4]	0.0001	4.23 [3.00; 6.33]	3.84 [3.40; 6.44]	0.781
NLR	6.05 [3.8; 11.2]	15.3 [6.62; 19.7]	0.006	4.06 [2.12; 5.45]	3.04 [2.12; 8.98]	0.890
Platelets, 10^9/l	216 [179; 248]	280 [229; 347]	0.001	196 [158; 264]	356 [311; 420]	0.0001
Glucose, mmol/l	6.06 [5.10; 7.60]	7.16 [5.47; 9.96]	0.222	6.05 [5.78; 6.49]	4.70 [4.33; 5.29]	0.032
Creatinine, µmol/l	91.0 [86.0; 102]	81.0 [67.5; 93.8]	0.088	82.0 [64.0; 105]	82.0 [72.0; 91.0]	0.477
GFR, ml/min/1.73 m²	78.0 [63.0; 87.0]	85.5 [80.5; 93.8]	0.088	76.0 [65.0; 98.0]	86.0 [67.0; 98.0]	0.448

CRP, C-reactive protein; GFR, glomerular filtration rate; CT, computed tomography.
The quantitative data are expressed as the median and interquartile range.

The NLR, which is an important parameter reflecting the severity of chronic inflammation, increased by 153% in the GC treatment group (p=0.006) and decreased insignificantly in the control group. The median change was + 6.12 [−16.5; + 0.34] in the GC treatment group vs. −0.315 [−1.73; +5.17] in the control group (p=0.038). Among the other parameters, a significant increase in platelet counts in both groups is noteworthy, which is quite good considering the aggressive anticoagulant therapy.

Changes in glucose levels were oppositely directed: an insignificant increase in the GC treatment group (p=0.222) and a significant decrease in the control group (p=0.032). The median changes were −1.02 [−1.63; −0.55] mmol/l in the control group and + 0.02 [−1.13; +3.15] mmol/l in the GC treatment group. These differences were not significance (p=0.06). However, 7 of 17 (41.2%) patients in the GC treatment

group had increased glucose of more than 9 mmol/l, which required ordering/enhancing the hypoglycemic therapy. There were no such cases in the control group. No significant changes in kidney function, creatinine levels, and GFR were found in either group.

The mean time of inpatient treatment was 18.0 [16.0; 20.5] days in the control group and 26.0 [22.0; 31.5] days in the GC treatment group (p=0.001).

We present a case report of a 62-year-old patient A. with COVID-19 and 68.2% pulmonary involvement according to the CT findings (Figure 6). The patient was observed for a long period. The CRP levels were 122 mg/dL, D-dimer 1.33 µg/ml, SpO$_2$ 89% without oxygen therapy. Severely decreased lymphocyte counts (0.34x109/l), increased neutrophil counts (6.26x109/l), and an extremely high NLR (18.4) were noticeable as markers of severe inflammation and VTE risk. The patient was transferred to the ICU and put on

Figure 6. CT angiopulmonography (a – transverse plane, b – frontal plane)
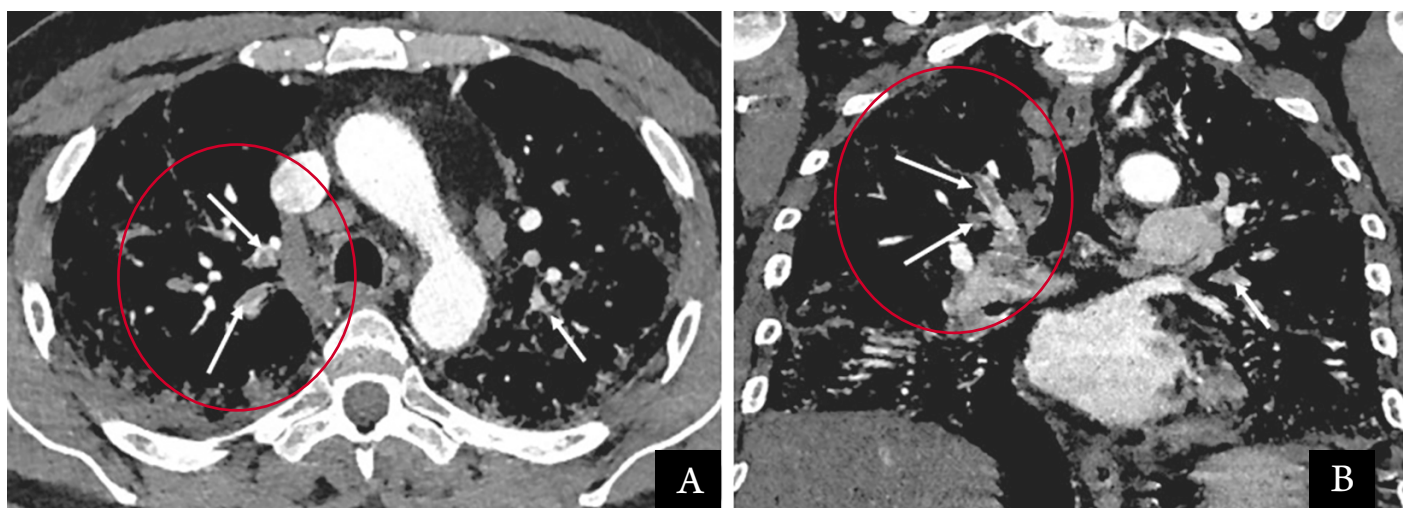
The arrows show contrast defects in the branches of the right upper lobar artery.

non-invasive lung ventilation. It was decided to conduct pulse GC therapy with high doses of GCs. After 5 days of the treatment, the patient's condition improved, body temperature decreased to normal, CRP level decreased to 46 mg/dl, oxygen saturation increased to 95%, and the degree of pulmonary involvement decreased to 38.2%. The patient was transferred from the ICU. Although lymphocyte counts remained decreased (0.37x109/l), the NLR increased to 20.6, and D-dimer increased to 2.74 µg/ml. The patient rapidly deteriorated the next day. Shortness of breath became extremely severe, chest pain occurred, and the D-dimer level increased to 13.52 µg/ml. CT angiography showed PE despite the continuous administration of LMWH in therapeutic doses. The dose of LMWH was further increased, and dipyridamole was added. Subsequently, all the complications were successfully reversed, and the patient was discharged from the hospital in good condition on Day 27.

Discussion

COVID-19 passes through several stages, each requiring specific treatment. At the onset of viral pneumonia with alveolar lesions, the problem becomes more severe because of the progression of systemic inflammation and the involvement of pulmonary parenchyma, bronchioles, and small vessels, as well as increased clotting. In these cases, hyper-reactivity of the immune system is accompanied by excessive activation of cytokines, further activation of macrophages and epithelial cells, and a constant increase in the release of cytokines and chemokines, i.e., a cytokine storm [14, 15]. The objective of this study was to evaluate the treatment of this category of patients with COVID-19. The Guidelines of the WHO and the Russian Ministry of Health suggest using preventive anti-inflammatory therapy in such cases to arrest the cytokine storm and overcome critical inflammation [2, 3]. Given the significant role of pro-inflammatory ILs, the IL-6 inhibitor, tocilizumab [16], the IL-1β inhibitor, canakinumab [17], the IL-17 inhibitor, secukinumab [18], the JAK-1 and JAK-2 Janus-kinase inhibitors, ruxolitinib [19], are recommended as anti-inflammatory agents. Even with possible high efficacy of these agents, which is yet to be verified in clinical studies, their availability and cost leave much to be desired.

Although the most popular anti-inflammatory agents in the past 50 years, GCs are not recommended by the WHO in COVID-19, and only the 7th version of the Russian Ministry of Health Guidelines included the possible use of low doses of GCs (1 mg/kg/day). A meta-analysis of studies on the use of corticosteroids in coronavirus pneumonia, including COVID-19, showed no positive effect on prognosis and they slowed-down elimination of the virus [20, 21]. However, the early pulse therapy with high-dose GCs in atypical pneumonia decreased progression of the disease and improved resolution of alterations in the pulmonary structures with low risk of side effects [22, 23]. GC therapy is limited by its ability to enhance prothrombotic factors, especially in immune inflammation, which occurs in COVID-19 with the cytokine storm [24]. Several studies associate the risk of VTE development during corticosteroid therapy with dose level, and the maximum increase in risk is observed with doses from 1000 to 2000 mg/day. [25]. The main danger of GC therapy is that the risk of thrombosis and thromboembolism occurs immediately after the start of treatment [26].

Given the ambiguities and insufficient knowledge regarding this issue, the objective of our study was to assess the balance of efficacy and safety of pulse GC therapy (intravenous methylprednisolone 1000 mg for 3 days followed by dexamethasone mg for 3–7 days) for the treatment of patients with severe coronavirus pneumonia in comparison to the group of patients who did not receive the anti-inflammatory therapy. Examinations of patients showed signs of systemic inflammation with an extreme 19-fold increase in the CRP levels, a marker of the cytokine storm, in the control group and a 27-fold increase in the GC treatment group. Fever, low lymphocyte counts (0.66x109/l), high neutrophil counts (5.02x109/l), and increased NRL (6.05), a threefold increase in D-dimer levels, shortness of breath (RR 26 breaths per min) with SpO_2 (85%), tachycardia (HR 97 bpm) were detected in the GC treatment group. The cumulative NEWS-2 clinical score, which includes treatment in the ICU (70.6%) and AV (35.3%), and confusion, as well as the clinical manifestations of the disease, was 11. A score of more than 7 corresponds to very high risk. The degree of pulmonary involvement was more than 50%, which corresponded to stage 3, according to the Russian Ministry of Health Guidelines. The cumulative SHOKS-COVID score, which includes the CRP and D-dimer levels and the volume of pulmonary tissue lesions, as well as clinical parameters, and takes into account the predictive factors, was 13 in patients in the GC treatment groups, which corresponded to a high risk of an unfavorable outcome Patients in the control group had a less severe course of the disease, according to most of the parameters examined. On one hand, that made it difficult to compare results in both groups, but on the other hand, it gave us hope for a more favorable course of the disease.

The study confirmed the possible efficacy of pulse GC therapy in COVID-19 pneumonia complicated by a cytokine storm. The SHOKS-COVID score, the primary endpoint of the study, decreased significantly and more than in the control group. There was a significant improvement in the clinical condition as indicated by NEWS-2 score 8, oxygen saturation +9%, body temperature back to normal values, and significant reduction in the need for oxygen therapy. This improvement was accompanied by a threefold decrease in the CRP levels, which characterized the rapid anti-inflammatory effect of high doses of GCs. As a result, the degree of pulmonary involvement did not change, unlike in the control group, where pneumonia progressed and the degree of pulmonary involvement significantly increased. The case report of patient I shows the progression of pulmonary involvement in the absence of anti-inflammatory therapy in the first period of treatment (Figures 5.01, 5.02) and the resolution of the process after pulse GC therapy in the second period of observation (Figures 5.02, 5.03). To a certain extent, this is a remarkable clinical illustration of the comparative effect of control (no anti-inflammatory therapy, the first period) and pulse GC therapy (the second period) in the same patient. That was one of the first severe patients with COVID-19 in our hospital, and that experience taught us that the course of COVID-19 pneumonia is extremely persistent and cannot be treated successfully without anti-inflammatory agents if markers of inflammation are increased. The findings demonstrated that pulse GC therapy could interrupt the cytokine storm. However, the results of the studies on COVID-19 did not confirm an improvement of the prognosis, but rather the opposite [27, 28]. Thus, recommendations were made to use anti-cytokine agents rather than GCs, which could also slow down the elimination of the virus during the treatment of COVID-19 [29, 30].

The second objective of the study was to assess the safety of high-doses pulse GC therapy in patients with COVID-19. We did not find adverse effects on cardiological parameters, including an increase in BP. There was also no increase in the glucose levels in the GC treatment group on average, although this parameter decreased significantly in the control group. The personified analysis showed that 6 of 17 (35.3%) patients had increased glucose levels of more than 9 mmol/l, which required ordering/enhancing hypoglycemic therapy. The changes in the D-dimer level posed the main problem. This parameter did not change in the control group and increased significantly (median up to 1.98 μg/ml) in the GC treatment group. Several

Figure 7. Correlations between the changes in NLR and D-dimer
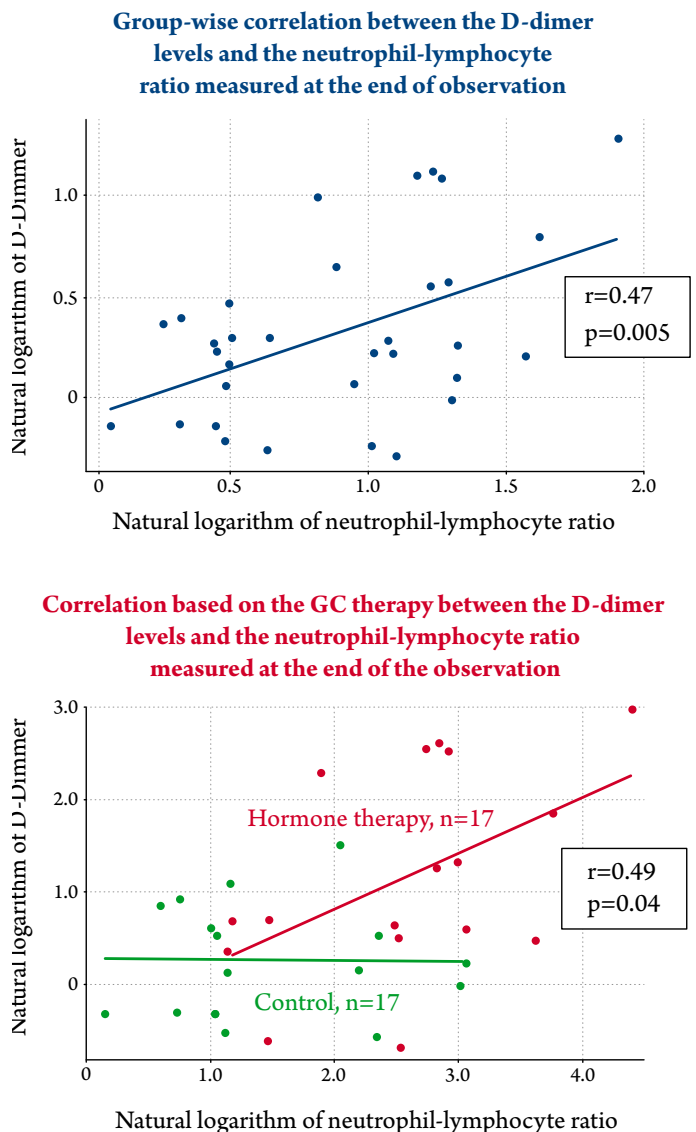
studies demonstrated that the increased D-dimer levels of more than 2.0 μg/ml increased 51-fold the risk of VTE in patients with COVID-19 [31]. Other studies showed that even an increase in the D-dimer levels of more than 1.0 μg/ml significantly increased by 18-fold the risk of thrombosis [32]. In our study, 4 patients had venous thrombosis (2 PEs) associated with an increase in the D-dimer levels of more than 10 μg/ml. Given the fact that thrombotic complications in COVID-19 are related to autoimmune inflammation, we analyzed the possible relationships. GCs are known to increase leukocyte and neutrophil counts [33]. In our study, neutrophil counts increased by 73% (p<0.0001) in the GC treatment group and did not change in the control group.

The NLR statistically significantly increased by 2.5-fold with leukocyte counts remaining unchanged, and no changes were observed in the control group. The NLR

reflects the activation of chronic inflammation [34, 35], including autoimmune endothelial inflammation [36], and it characterizes the adverse course of COVID-19 [37, 38]. Therefore, we analyzed the correlation between changes in the NLR and the D-dimer levels during the treatment (Figure 7).

As can be seen in Figure 7, there was a direct, significant correlation between an increase in the D-dimer levels and the NLR in In all 34 investigated patients (r=0.47, p=0.005) and the GC treatment group (r=0.49, p=0.04). The was no such correlation in the control group. It should be especially noted that the NLR is not only a marker of inflammation but is also a predictor of VTE and PE [39, 40]. A study including 180 patients with COVID-19 demonstrated a close statistically significant relationship between the NLR and the degree of pulmonary involvement according to CT findings [41]. Thus, despite the rapid reduction in the CRP levels and acute inflammation, as well as the clinical improvement in patients with COVID-19, the use of GCs increases neutrophil counts and the NLR. This results in a significantly higher risk of thrombosis as demonstrated by a significant increase in the D-dimer levels. The use of the NLR can predict both the severity of the COVID-19 course [42] and an unfavorable prognosis [43]. The risk of a lethal outcome in patients with coronavirus pneumonia increases 15-fold [44] with an increase in the NLR to maximum values (4.85–88.09), and the efficacy of GCs decreases with high NLR [45]. Therefore, it is necessary to take into account the NLR and the D-dimer levels and consider the enhancement of anticoagulant therapy when using high-dose pulse GC therapy as an anti-inflammatory treatment of the cytokine storm in patients with COVID-19.

Moreover, the recovery of lung airiness may be delayed [41, 46] if the NLR and chronic inflammation increase. This may extend the duration of treatment. Patients in the GC treatment group spent 8 days more in the hospital, although that may be partially explained by a more severe course of the disease. We order a course of the anti-inflammatory inflammasome inhibitor, colchicine, after the GC therapy to accelerate recovery, as is shown in our second case report. The clinical efficacy of this is currently being investigated (https://clinicaltrials.gov/ct²/show/NCT04403243).

Limitations of the study

A small number of patients was included in the study. The retrospective design of the study precluded randomization. There were intergroup differences in the baseline characteristics.

No conflict of interest is reported.

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