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Proactive anti-inflammatory therapy with colchicine in the treatment of advanced stages of new coronavirus infection. The first results of the COLORIT study

Actuality	The course of the novel coronavirus disease (COVID-19) is unpredictable. In some cases, it manifests as increasing inflammation that leads to a cytokine storm and irreversible progression to acute respiratory syndrome, which is associated with the risk of death. Thus, proactive anti-inflammatory therapy remains an open, serious question for patients with COVID-19 and pneumonia. This is especially true for those patients who still have signs of inflammation on days 7–9 of the disease. These signs include elevated C-reactive protein (CRP) >60 mg/dl and at least two of the four clinical signs: 1) fever >37.5°C; 2) persistent cough; 3) dyspnea (RR >20 brpm) and/or reduced arterial oxygen saturation (SaO_2) <94% when breathing atmospheric air. We designed the randomized trial: COLchicine versus Ruxolitinib and Secukinumab in Open-label Prospective Randomized Trial in Patients with COVID-19 (COLORIT). We present here data comparing patients who received colchicine with those who did not receive this specific anti-inflammatory therapy. Results of the comparison of colchicine, ruxolitinib, and secukinumab will be presented later.
Objective	Compare efficacy and safety of colchicine in the management of patients with COVID-19 to that without specific anti-inflammatory therapy.
Material and Methods	Initially, 20 people were expected to be randomized in the control group. However, enrollment to the control group was discontinued after the inclusion of 5 patients due to the risk of severe deterioration in the absence of anti-inflammatory treatment. Therefore, 17 patients, who had not received anti-inflammatory therapy when previously treated in the MSU Medical Research and Educational Center, were also included in the control group. The effects of treatment were assessed on day 12 after inclusion or at discharge if discharge occurred earlier than on day 12. The primary endpoint was changes in the SHOCS-COVID score, which includes an assessment of the patient's clinical condition, CT score of lung tissue damage, the severity of systemic inflammation as indicated by changes in CRP, and the risk of thrombotic complications as indicated by D-dimer [1].
Results	In the colchicine group, the median SHOCS score decreased from 8 to 2 (p=0.017), i.e., from a moderate to a mild degree. In the control group, the change in the SHOCS-COVID score was minimal and statistically insignificant. In patients treated with colchicine, CRP decreased rapidly from 99.4 and normalized at 4.2 mg/dl (p<0.001). In the control group, CRP decreased moderately but insignificantly and was 22.8 mg/dl by the end of the 12 day follow-up period. This CRP value was still more than 4 times higher than normal. The most informative criterion for inflammation, the lymphocyte-to-CRP ratio (LCR) increased in the colchicine group by 393 versus 54 in the control group (p=0.003). After treatment, the LCR was 60.8 in the control group, which was less than 100, which is considered safe in terms of systemic inflammation progression. The difference from 427 in the colchicine group was highly significant (p=0.003). The marked and rapid decrease in the inflammation factors was accompanied in the colchicine group by the number of patients needing oxygen support, which decreased from 14 (66.7%) to 2 (9.5%). In the control group, the number of patients requiring oxygen support remained unchanged at 50%. There was a trend for shorter hospital stay in the colchicine group, with median stay of 13 days compared to 17.5 days in the control group (p=0.079). Moreover, two patients died in the control group, and there were no fatalities in the colchicine group. In the colchicine group, one patient had deep vein thrombosis with D-dimer elevated to 5.99 μg/ml. This condition was resolved before discharge.

Conclusions Colchicine 1 mg for 1–3 days followed by 0.5 mg/day for 14 days is effective as a proactive anti-inflammatory therapy in hospitalized patients with COVID-19 and viral pneumonia. The management of such patients without proactive anti-inflammatory therapy is likely to be unreasonable and may worsen the course of COVID-19. However, the findings should be treated with caution, given the small size of the trial.

Keywords COVID-19; colchicine; SHOCS-COVID; NEWS-2; CRP

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The pandemic of the novel coronavirus disease (COVID-19) has remained one of the main medical issues for more than a year. Vaccination should change this picture and reduce the number of infected patients, but it does not detract from the need to find effective ways to treat this severe and often unpredictable viral disease. The mortality rates have averaged around 2% in recent months, and initial differences across countries have decreased significantly [2]. This was made possible through the widespread introduction of glucocorticoids (GCs) and anticoagulants into the treatment of COVID-19 patients. However, the need for proactive anti-inflammatory therapy remains a serious and open issue. There are two polar approaches, both of which can be potentially dangerous. The first one is to minimize the disease severity and treat it as an acute viral respiratory infection as when the body and immunity must cope with the disease without any intervention from health care providers. As a result, patients who do not improve by the beginning of week 2 of the disease are then admitted to hospitals with extensive lung tissue damage and cytokine storm.

The second approach of some medical professionals was to not waste time on anti-inflammatory drugs and to use all available tools when patients are admitted to an intensive care unit. These include mechanical ventilation, extracorporeal membrane oxygenation, interleukin (IL) – 6 blockers, antibiotics, plasma from recovered COVID-19 patients, etc. The consistent position of the MSU Medical Research and Educational Center, which was formulated in May 2020, is the strict phasing of treatment: 1) antiviral therapy and treatment aimed to prevent virus replication or its penetration into cells at an early stage, e.g., bromhexine in combination with spironolactone [3, 4]; 2) proactive anti-inflammatory therapy if there is no improvement by day 7–9 [5]; 3) high-dose GC pulse therapy in critical patients with cytokine storm [6].

The use of colchicine, a well-known drug used to treat acute gout attacks, as a proactive anti-inflammatory treatment may be of great, current interest [7, 8]. Attention to colchicine in recent years has continued. Its efficacy was shown in patients with a history of acute myocardial infarction [9] and chronic coronary artery disease [10]. The anti-inflammatory effects of colchicine are implemented through several mechanisms, primarily through the inhibition of inflammasomes [11]. Pyroptosis, i.e., programmable cell death causing inflammation, and production of IL-1β and IL-18 cytokines are reduced when inflammasomes are inhibited, and the activity of the cascade mechanism is decreased [12].

As a result, colchicine has anti-inflammatory potential in various triggering conditions, such as, atherosclerosis, hyperuricemia, and viral infection, and can prevent the cytokine storm [13–15]. Moreover, colchicine can inhibit intracellular replication of the SARS-CoV-2 virus when it binds to the intracellular protein, tubulin, that forms microtubules [16]. We have published the first successful results of using colchicine in COVID-19 and in the design of the COLORIT trial (COLchicine versus Ruxolitinib and Secukinumab in Open-label Prospective Randomized Trial in Patients with COVID-19) [5]. The first completed randomized trial of colchicine in patients with COVID-19, GRECCO-19, increased hope that it is a potential cure for this disease [17]. The use of colchicine shortened the time to the normalization of the clinical condition in the hospitalized patients. However, there was no significant decrease in CRP as a marker of inflammation.

Colchicine is one of the most studied COVID-19 treatment drugs, and it is now under several randomized control trials, including the RECOVERY trial (UK) of using colchicine in hospitalized patients [18] and the international trial with Russian involvement,

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ACTCOVID19 [19], in which both ambulatory and hospitalized patients are included.

At the end of January 2021, the COLCORONA trial was published [preprint, 20], in which colchicine was administered outside the hospital, 0.5 mg twice-daily for the first 3 days, then daily for 27 days. The analysis of all 4,488 COVID-19 patients revealed a trend for decreasing the risk of death or hospitalization due to COVID-19, although this trend did not achieve statistical significance (odds ratio (OR) 0.79, 95% CI 0.61–1.03), p=0.08). However, an analysis of 4,159 patients (92.7% of the all included patients) who tested positive by PCR showed a decrease in the composite endpoint of death or hospitalization due to COVID-19 by 25% (OR 0.75, 95% CI 0.57–0.99), p=0.04

In this article, we report the results of using colchicine at a later stage in patients hospitalized with COVID-19, using the same approach of proactive anti-inflammatory therapy as utilized in the COLORIT trial, the design of which was published earlier [5, 21].

Material and Methods

The COLORIT trial was designed as a prospective, comparative trial with patients randomized to four groups. The control group (n=20) received no proactive anti-inflammatory therapy. The colchicine group (n=20) received 1 mg colchicine during the first 1–3 days followed by 0.5 mg/day. Two other biological drugs were also studied: 1) secukinumab, a human monoclonal antibody (immune globulin IgG1), which selectively binds to and neutralizes the pro-inflammatory cytokine IL-17A, a single dose of 300 mg/day subcutaneously (n=20); 2) ruxolitinib, a selective inhibitor of Janus kinases (JAK 1 and JAK 2), which mediate cytokines (including IL-6) signaling at the dose of 5 mg twice daily (n=10). The effect was assessed on day 12 after the inclusion or at discharge if discharge occurred earlier than day 12 and, if possible, on day 45 days after discharge from the hospital.

The three treatment groups were completely randomized, but only 5 patients were initially randomized to the control group. Later, enrollment to the control group was discontinued due to the severity of the course of the disease and the risk of rapid progression of COVID-19. Thus, 17 patients, who had not received anti-inflammatory therapy when they had been treated previously in the MSU Medical Research and Educational Center before the study, were additionally included in the control group. This article presents a controlled study of using colchicine to treat patients with the novel coronavirus pneumonia during the hospital stay.

The inclusion criteria were as follows:

- Proven coronavirus pneumonia (positive PCR for SARS-CoV-2 RNA and/or clear specific presentation of pneumonia: diagnoses U07.1 and U07.2).
- Signs of inflammation and elevated CRP >60 mg/l.
- Additionally, at least two of the following four signs: fever >37.5°C; persistent cough; dyspnea with the respiratory rate (RR) >20 brpm and/or SaO_2 <94% when breathing atmospheric air.

The primary endpoint was the change in the SHOCS-COVID score, which includes the assessment of the patient's clinical condition, computed tomography (CT) score of the lung tissue damage, the severity of systemic inflammation as reflected in CRP changes, and the risk of thrombotic complications as reflected by D-dimer [1]. The study included 43 patients, 21 patients in the colchicine group and 22 patients in the control group (Table 1).

Both mean and median values are provided for the NEWS2 and SHOCS-COVID scores. SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; RR, respiratory rate; HR, heart rate; SaO_2, oxygen O_2 saturation; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; GFR, glomerular filtration rate; SBP, systolic blood pressure; CT, computed tomography.

The groups were balanced. Subfebrile body temperature, dyspnea with increased RR >18 brpm, and reduced SaO_2 requiring oxygen support were observed in 66.7% of the colchicine cases and 54.5% of the control cases. At the same time, in both groups, pronounced inflammatory reactions were observed as well as decreased lymphocyte count, an 18–20-fold increase in CRP and a sharp decrease in the lymphocytes-to-CRP ratios as indicators of the severity of systemic inflammation [22]. The total NEWS-2 score, which characterizes the patient's clinical status became close to the values for which it is recommended to consider moving patients to the intensive care unit (ICU). Similar trends were observed for the original SHOCS-COVID score, according to which the course of the disease could be defined as moderate-to-severe. Thus, the proactive therapy was necessary and appropriate for the included patients to improve their prognosis, slow down the disease progression, prevent the risk of a cytokine storm, and to reduce the need for oxygen support and the risk of admission to the ICU.

Table 1. Baseline patient characteristics

Parameters	Colchicine (n=21)	Control (n=22)	p
General characteristics			
Age, years, mean (SD)	61.9 (10.6)	59.9 (18.8)	0.677
BMI, kg/m^2; mean (SD)	30.2 (3.59)	30.6 (5.37)	0.788
Male, n (%)	14 (66.7)	16 (72.7)	0.920
Arterial hypertension, n (%)	14 (66.7)	13 (59.1)	0.843
CAD, n (%)	3 (14.3)	4 (18.2)	1.000
Diabetes mellitus, n (%)	3 (14.3)	2 (9.09)	0.660
Clinical characteristics			
Body temperature, mean (SD)	37.5 (0.69)	37.1 (0.85)	0.139
RR per minute, median [25%; 75%]	18.0 [17.0; 20.0]	19.0 [18.0; 21.8]	0.269
HR, bpm, median [25%; 75%]	76.0 [72.0; 82.0]	81.0 [74.2; 87.8]	0.193
SBP, mm Hg, median [25%; 75%]	120 [112; 120]	125 [115; 129]	0.311
SaO_2, %, median [25%; 75%]	93.0 [92.0; 96.0]	94.5 [93.0; 96.0]	0.497
Any oxygen support, n (%)	14 (66.7)	12 (54.5)	0.617
Laboratory parameters			
CRP, mg/l, median [25%; 75%]	99.4 [57.7; 116]	91.5 [59.2; 131]	0.903
D-dimer, μg/ml, median [25%; 75%]	0.87 [0.58; 1.24]	1.12 [0.79; 1.37]	0.185
Fibrinogen, g/l, mean (SD)	5.84 (1.70)	6.46 (1.23)	0.201
Lymphocytes, x10^9/l, median [25%; 75%]	0.99 [0.83; 1.34]	1.06 [0.79; 1.55]	0.865
Neutrophils, x10^9/l, median [25%; 75%]	2.99 [2.56; 4.62]	4.47 [3.07; 5.64]	0.065
NLR, median [25%; 75%]	2.93 [2.39; 3.65]	3.53 [2.03; 6.24]	0.437
Platelets, x10^9/l, mean (SD)	220 (91.1)	216 (74.5)	0.897
LCR, median [25%; 75%]	14.0 [8.01; 22.5]	12.5 [7.88; 21.9]	0.884
Glucose, mmol/l, mean (SD)	5.74 (1.03)	6.05 (0.81)	0.303
Creatinine, μmol/l, mean (SD)	89.3 (20.5)	86.6 (25.0)	0.705
GFR (CKD EPI) mL/min/1.73 m^2, mean (SD)	75.2 (18.1)	81.1 (25.6)	0.383
Total severity score			
CT lung damage (%), mean (SD)	22.1 (16.1)	26.0 (12.8)	0.410
NEWS-2, score, mean (SD)	4.95 (2.66)	4.85 (2.68)	0.910
NEWS-2, score, median [25%; 75%]	5.00 [3.00; 7.00]	5.00 [3.75; 7.00]	0.865
SHOCS-COVID, score, mean (SD)	7.21 (2.15)	7.71 (2.61)	0.508
SHOCS-COVID, score, median [25%; 75%]	8.00 [6.00; 8.50]	7.00 [6.00; 10.0]	0.773
Treatment, n (%)			
Glucocorticoids	–	–	0.089
Oral, n (%)	2 (9.52)	0 (0.00)	–
Inhaled, n (%)	1 (4.76)	0 (0.00)	–

All patients in both groups received antibacterial therapy and anticoagulants following the treatment protocol adopted in the MSU Medical Research and Educational Center from the first day as a COVID-19 hospital. Three patients in colchicine group received small-dose GCs: oral (n=2) and inhaled (n=1) with concomitant chronic obstructive pulmonary disease).

Methods of Examination

The following laboratory tests were done:

- 1) blood biochemical profile (CRP, creatinine, urea, glucose), automatic biochemical analyzer AU480 (Beckman Coulter, Germany;
- 2) complete blood count, hematological analyzer XN 2000 (Sysmex Corporation, Japan);
- 3) hemostasis analysis (fibrinogen, D-dimer), hemostasis analyzer STA-Compact (Diagnostica Stago SAS, France);
- 4) IL-6, Cobas 6000 immunochemistry analyzer (Roche Diagnostics GmbH, Germany).

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Lung and chest CT scans were produced using a 32 slice SOMATOM Scope CT scanner (Siemens, Germany). The scans were obtained with 1-mm slices. A detailed description of the CT scan procedure in patients with COVID-19 in our center has been published [4].

We used two scores to objectively determine the severity of the clinical condition and evaluate adequately the effects of the therapy: The National Early Warning Score (NEWS) of the severity of acute respiratory distress syndrome [23] modified for patients with COVID-19 [24] and the original Symptomatic Hospital and Outpatient Clinical score for COVID-19 (SHOCS-COVID) published earlier [1].

Statistical Analysis

Statistical analyses were performed using the R programming language in R Studio. The normality of distributions was evaluated with the Shapiro-Wilk test. Quantitative data are described as the median and the interquartile range (25%; 75%) if the distribution was non-normal and as the mean and the standard deviation if the distribution was normal. Qualitative indicators were compared between the groups with the Mann-Whitney test for non-normal distributions and with the Student's t-test for normal distributions.

Qualitative data are presented as absolute and relative values. The significance of intergroup differences in qualitative characteristics was assessed with the χ^2 test and the two-tailed Fisher's exact test.

Changes in variables were compared within each group with the Wilcoxon signed-rank test if not normally distributed and with the paired Student's t-test if normally distributed. The McNemar test was used for qualitative indicators. Correlations were estimated using Spearman's correlation coefficient. The threshold for statistical significance was 0.05.

Results

All main findings in the colchicine and control groups are presented in Table 2.

As mentioned above, the primary endpoint was changes in the SHOCS-COVID score, which included assessment of the patient's clinical condition, CT score of lung tissue damage, the severity of systemic inflammation as reflected by CRP changes, and the risk of thrombotic complications as indicated by D-dimer values. These results are provided in Table 2 and Figure 1A. In the colchicine group, the median SHOCS score decreased significantly from 8 to 2 (p=0.017), i.e., from a moderate to a mild degree. In the control group, the change in the SHOCS-COVID score was minimal and insignificant. Scores of the two groups differed significantly (p=0.002) by the end of the follow-up period.

Changes in COVID-19 patients' clinical status were analyzed using the total NEWS – 2 score (Table 2). In the colchicine group, the NEWS-2 score decreased significantly by more than 3 (p<0.001), but in the control group, changes were minimal and insignificant. Changes in the clinical condition were statistically significant and more pronounced in the colchicine group (p=0.009).

The main components of clinical severity are fever, dyspnea, SaO_2, and the need for oxygen support (Table 2). Body temperature decreased significantly in both groups, by 1.05°C in the treatment group and by 0.48°C in the control group. It normalized in all cases. RR, characterizing dyspnea, decreased significantly in the treatment group but insignificantly in the control group. By the end of follow-up RR was 16 in colchicine group and 18 in the control group (p=0.002).

Figure 1. Changes in the general severity of COVID-19 manifestations as indicated by the SHOCS-COVID score and changes the clinical severity of the disease as indicated by the NEWS-2 score in the colchicine and control groups

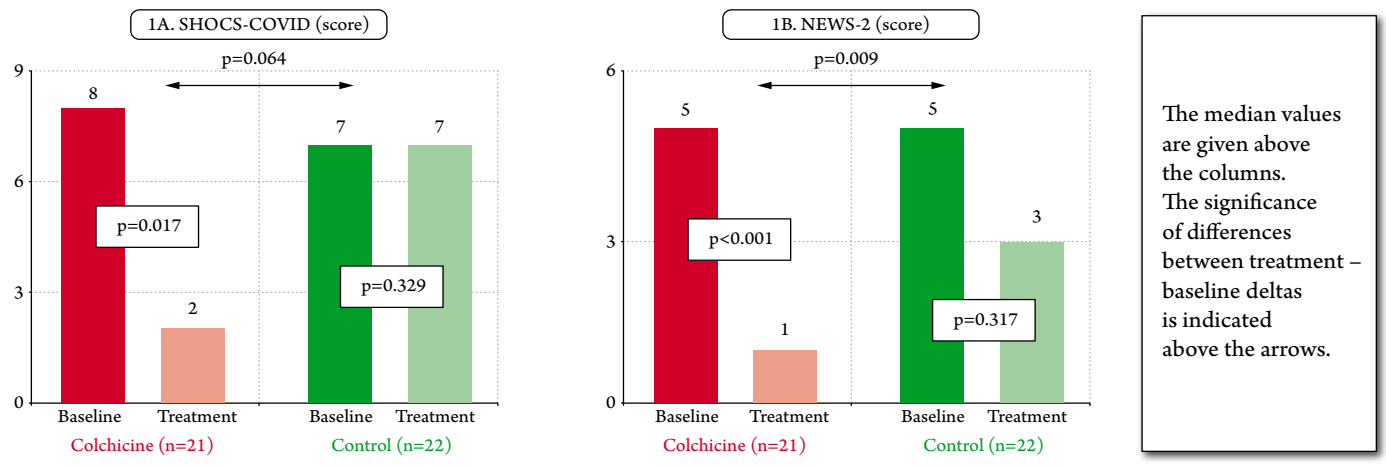
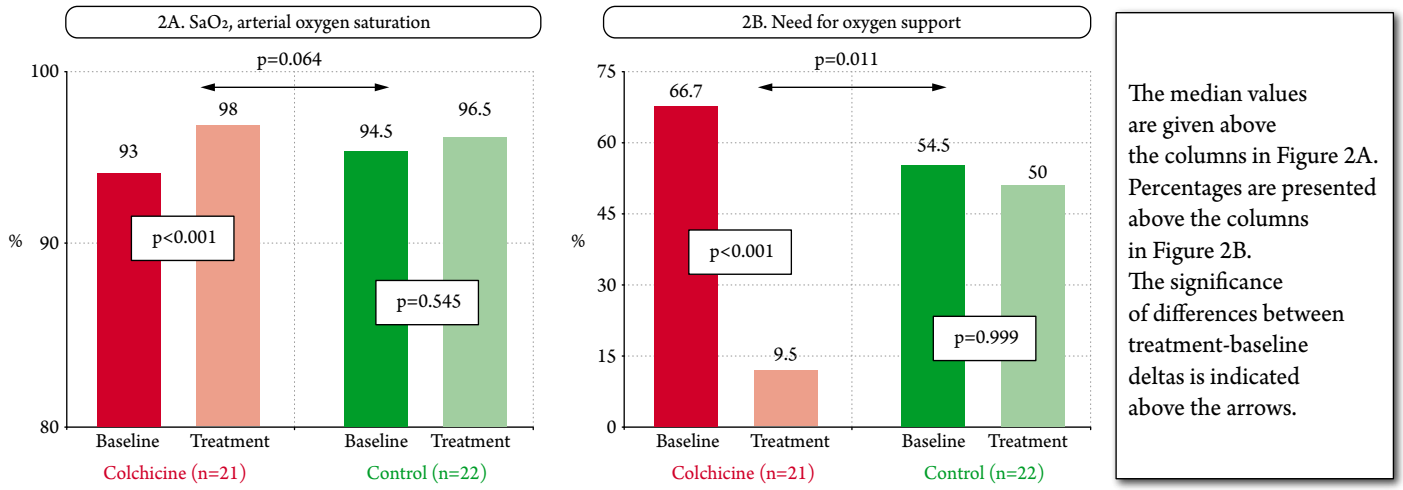


Figure 2. Changes in SaO_2 and the need for oxygen support in COVID-19 in the colchicine and control groups



Changes in HR were insignificant in both groups. However, by the end of the follow-up period, HR was 74 bpm in the colchicine group versus 80 bpm in the control group (p=0.027). Changes in BP were minimal and remained within normal limits.

There was substantial differences in the way how SaO_2 had changed in the groups (Table 2 and Figure 2A). The increase in SaO_2 when breathing atmospheric air was significant in the colchicine group (SaO_2 reached 98%) and insignificant in the control group. The resulting median SaO_2 of the control group was 96.5% (p=0.014 compared to the colchicine group). At baseline, SaO_2 <94% was found in 10 (52.6%) patients in the colchicine group. This number decreased to 1 (5.0%) by the end of the follow-up. In the control group, 6 (30%) patients had SaO_2 <94% at baseline, and that number did not change by the end of follow-up. Thus, the need for oxygen support/ventilation (Table 2 and Figure 2B) decreased prominently and significantly from 66.7% to 9.5% (p<0.001) in the colchicine group but remained virtually unchanged in the control group. 50% of control patients were still unable to breathe independently in order to ensure adequate SaO_2.

Assessing the inflammatory status, the risk of a cytokine storm, and the irreversible progression of coronavirus pneumonia are among the main challenges in treating COVID-19 patients. A severe decrease in lymphocyte count is the most accessible indicator. Its reversal usually corresponds to transition toward recovery. Lymphocyte count increased significantly in both groups but the increase was significantly higher in the colchicine group (p=0.008). CRP is a much more accurate indicator of the degree of inflammation (Table 2 and Figure 3 A), along with changes in LCR (Table 2, line 16 and Figure 3B).

The use of colchicine in COVID-19 was associated with a rapid and statistically significant decrease and normalization of CRP (from 99.4 to 4.2 mg/dl, p<0.001). In the control group, CRP decreased moderately and insignificantly and was 22.8 mg/dl by the end of the follow-up period. This was still more than 4 times higher than normal and significantly lower than in the colchicine group.

LCR increased significantly in both groups, but the intergroup difference was very significant. The delta in the colchicine group was 393 versus 54 in the control group (p=0.003). After treatment, this delta was 60.8 in the control group, which was less than the 100 considered safe in terms of systemic inflammation progression. The difference from 427 in the colchicine group was highly significant (p=0.003).

Progressive, systemic inflammation accompanied by endothelial dysfunction and increased thrombosis is one of the main pathogenetic mechanisms of COVID-19 progression and the development of thrombotic and thromboembolic complications. Trends in D-dimer and fibrinogen should be analyzed to evaluate these changes in the course of proactive anti-inflammatory therapy. The neutrophil-to-lymphocyte ratio (NLR) is also closely correlated with the risk of thrombotic and thromboembolic complications, which was demonstrated by the MSU Medical Research and Educational Center in the WAYFARER trial [6].

Changes in D-dimer and fibrinogen were statistically insignificant in both groups. However, D-dimer almost normalized to 0.66 μg/ml after colchicine and remained more than twice as high at 1.14 μg/ml in the control group, although these differences was insignificant. Changes in fibrinogen were more evident. There was a clear trend in the colchicine group for decreasing fibrinogen (p=0.061), but it hardly changed

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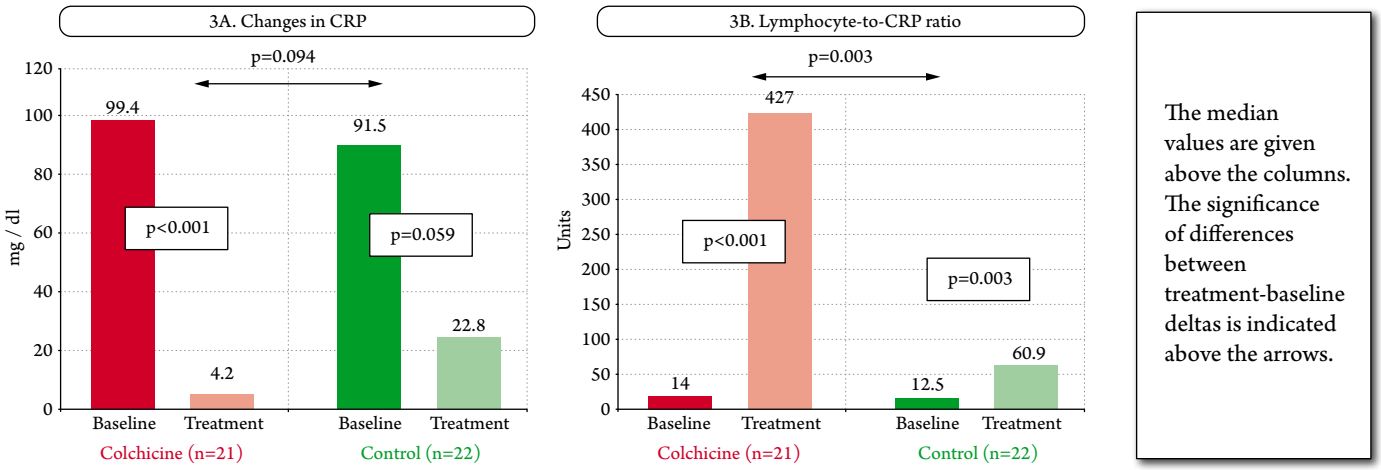
Table 2. Outcomes of patients treated with colchicine and control patients

Parameters	Colchicine (n=21)		Control (n=22)		p, intergroup differences
	Baseline	Treatment	Baseline	Treatment	Baseline/ Treatment
SHOCS-COVID, median [25%; 75%]	8.00 [6.00; 8.50]	2.00 [2.00; 3.25]	7.00 [6.00; 10.0]	7.00 [4.00; 9.00]	0.508/0.002*
Δ treatment – baseline, median [25%; 75%]	–4.00 [–6.00; –2.25] p=0.017*		–2.00 [–4.50; 2.00] p=0.329		0.064**
Body temperature, °C, median [25%; 75%]	37.4 [36.9; 37.8]	36.5 [36.2; 36.5]	36.9 [36.6; 37.6]	36.5 [36.3; 36.8]	0.139/0.425
Δ treatment – baseline, mean (SD)	–1.01 (0.75), p<0.001*		–0.48 (0.83), p=0.02*		0.035*
RR, brpm, median [25%; 75%]	18.0 [17.0; 20.0]	16.0 [16.0; 17.2]	19.0 [18.0; 21.8]	18.0 [17.0;19.0]	0.269/0.002*
Δ treatment – baseline, median [25%; 75%]	–2.00 [–4.00; – 1.00], p<0.001*		–1.00 [–3.00; 0.00], p=–0.066		0.297
HR, bpm, median [25%; 75%]	76.0 [72.0; 82.0]	74.0 [68.0; 76.0]	81.0 [74.2; 87.8]	80.0 [73.0; 85.8]	0.193/0.027*
Δ treatment – baseline, mean (SD)	–4.24 (10.9), p=0.121		–3.55 (16.7), p=0.159		0.873
SBP, mm Hg, median [25%; 75%]	120 [112; 120]	120 [120; 122]	125 [115; 129]	119 [111; 124]	0.311/0.380
Δ treatment – baseline, mean (SD)	–1.43 (16.6), p= 0.999		–4.82 (11.5), p=0.079		–
SaO_2, %, median [25%; 75%]	93.0 [92.0; 96.0]	98.0 [97.0; 99.0]	94.5 [93.0; 96.0]	96.5 [92.0; 98.0]	0.227/0.014
Δ treatment – baseline, median [25%; 75%]	4.00 [1.00;6.00], p<0.001*		2.50 [–2.50; 4.00], p=0.545		0.064**
Any oxygen support, n (%)	14 (66.7)	2 (9.52)	12 (54.5)	11 (50.0)	0.617/0.011*
	p<0.001*		p=0.999		–
CRP, mg/dl, median [25%; 75%]	99.4 [57.7; 116]	4.2 [2.47; 11.1]	91.5 [59.2; 131]	22.8 [7.62; 95.9]	0.903/0.002*
Δ treatment – baseline, median [25%; 75%]	–86.7 [–110.1; – 41.1], p<0.001*		–52.0 [–96.5; 21.2], p=0.059**		0.094 **
D-dimer, μg/ml, median [25%; 75%]	0.87 [0.58; 1.24]	0.66 [0.36; 1.21]	1.12 [0.79; 1.37]	1.14 [0.65; 2.07]	0.175/0.186
Δ treatment – baseline, median [25%; 75%]	–0.23 [–0.88; 0.19], p=0.393		–0.39 [–1.06; 0.42], p=0.169		0.738
Fibrinogen, g/l, mean (SD)	5.84 (1.70)	4.53 (1.59)	6.46 (1.23)	6.45 (1.47)	0.201/0.006*
Δ treatment – baseline, mean (SD)	–1.01 (1.84), p=0.061**		–0.30 (2.14), p=0.670		0.407
CT lung damage, %, median [25%; 75%]	17.5 [9.40; 31.7]	13.4 [6.95; 34.2]	25.6 [12.6; 35.8]	34.0 [15.5; 49.1]	0.410/0.041*
Δ treatment – baseline, median [25%; 75%]	–4.20 [–9.88; 2.22], p=0.252		8.15 [–2.95; 21.4], p=0.056		0.065**
Lymphocytes, × 10^9/l, median [25%; 75%]	0.99 [0.83; 1.34]	1.83 [1.50; 2.22]	1.06 [0.79; 1.55]	1.38 [1.03; 1.89]	0.865/0.067**
Δ treatment – baseline, mean (SD)	0.76 (0.28), p<0.001*		0.31 (0.67), p=0.046*		0.008*
Neutrophils, × 10^9/l, median [25%; 75%]	2.99 [2.56; 4.62]	2.89 [2.50; 4.21]	4.47 [3.07; 5.64]	3.79 [2.74; 6.17]	0.065/0.215
Δ treatment – baseline, median [25%; 75%]	0.08 [–0.75; 1.07], p = 0.708		–0.33 [–1.72; 1.46], p=0.808		0.734
Platelets, × 10^9/l, mean (SD)	220 (91.1)	351 (96.4)	216 (74.5)	372 (105)	0.897/0.498
Δ treatment – baseline, mean (SD)	131 (113), p<0.001*		155 (102), p<0.001*		0.465
NLR, median [25%; 75%]	2.93 [2.39; 3.65]	1.72 [1.27; 1.87]	3.53 [2.03; 6.24]	2.79 [1.63; 3.14]	0.437/0.029*
Δ treatment – baseline, median [25%; 75%]	–1.44 [–2.01; – 0.67], p<0.001		–0.81 [–3.21; 1.26], p=0.425		0.382
LCR, median [25%; 75%]	14.0 [8.01; 22.5]	427 [155; 731]	12.5 [7.88; 21.9]	60.9 [11.2; 216]	0.884/0.003
Δ treatment – baseline, median [25%; 75%]	393 [147;727], p<0.001*		54.4 [–1.48;205], p=0.003*		0.003 *
GFR (CKD-EPI) mL/min/1.73 m^2, mean (SD)	75.2 (18.1)	78.3 (17.2)	81.1 (25.6)	83.4 (22.7)	0.383/0.428
Δ treatment – baseline, mean (SD)	3.14 (15.6), p=0.368		2.55 (10.6), p=0.294		–
Glucose, mmol/l, median [25%; 75%]	5.64 [5.12; 6.27]	5.66 [5.24; 6.55]	6.19 [5.79; 6.55]	5.09 [4.67; 5.63]	0.303/0.083**
Δ treatment – baseline, mean (SD)	0.17 (1.22), p=0.922		–0.85 (0.98), p=0.012*		0.010 *
NEWS-2 score, median [25%; 75%]	5.00 [3.00; 7.00]	1.00 [0.00; 3.00]	5.00 [3.75; 7.00]	3.00 [2.75; 5.25]	0.901/0.017*
Δ treatment – baseline, mean (SD)	–3.05 (2.48), p<0.001*		–0.50 (3.28), p=0.317		0.009 *
Hospital stay, days, median [25%; 75%]	13.0 [11.0; 15.0] **		17.5 [12.5; 19.8] **		0.079**
Death, n (%)	0 (0%)		2 (9.09%)		0.467

* p < 0.05; ** p<0.1; SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; RR, respiratory rate; HR, heart rate; SaO2, arterial oxygen saturation; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-CRP ratio; GFR, glomerular filtration rate; SBP, systolic blood pressure; CT, computed tomography.

Figure 3. Changes in CRP and LCR in patients with the novel coronavirus disease in the colchicine and control groups



in the control group. Fibrinogen decreased almost to normal (4.53 g/l) in the colchicine group, which was significantly lower than in the group without anti-inflammatory treatment (6.45 g/l; p=0.006). NLR declined significantly only in the colchicine group (p<0.001), and the post-treatment value (1.72) was significantly lower than in the control group (2.79; p=0.029).

Changes in the volume of damaged lung tissue was estimated by special evaluation of the pulmonary CT findings, although improvement of the CT assessment of the lungs is known to occur relatively late with respect to anti-inflammatory effects of the treatment (Table 2). It should be noted that lung tissue damage decreased insignificantly by 4.2% in the colchicine group. Simultaneously, the area of the lung tissue damage increased by 8.2% in the control group, and this change almost reached statistical significance (p=0.056). Differences in the treatment deltas of lung damage trended toward statistical significance (p=0.065). Thus, the area of lung damage after treatment with colchicine was 13.4%, and this area was significantly less than the 34.0% observed in the control group (p=0.041).

Additional indicators included fasting glucose (Table 2), which was elevated at baseline, even though only 3 patients in the colchicine group and 2 patients in the control group had concomitant diabetes mellitus (DM). Fasting glucose remained at the normal upper limit of 5.66 mmol/l in the colchicine group, but there was a significant decrease in glucose to 5.09 mmol/l in the control group. However, the final difference between the groups was not significant p=0.083). Only 5 patients, 3 in the colchicine group and 2 in the control group, had fasting glucose above 7.0 mmol/l in the end of follow-up, specifically, those with concomitant DM.

Clear benefits of the proactive anti-inflammatory treatment with colchicine in patients with coronavirus pneumonia suggest that it may prevent the risk of disease progression (Table 2). There was a trend for shorter hospital stays in the colchicine group with a median stay of 13 days compared to 17.5 days for the control group (p=0.079). The number of patients requiring oxygen support/ventilation decreased from 50% to 9.5% (p=0.011). Moreover, in the control group, 2 patients died; there were no fatal cases in the colchicine group. One patient taking colchicine had deep vein thrombosis with D-dimer elevated to 5.99 μg/ml, which resolved before discharge. Gastrointestinal side effects, mainly diarrhea, were reported in 6 (28.6%) patients. Only 1 (4.8%) patient in the colchicine group and 3 (13.6%) patients in the control group required treatment.

Discussion

The trial had two main objectives: 1) Determine the necessity of proactive anti-inflammatory therapy in patients with novel coronavirus disease who are hospitalized with viral pneumonia and persistent symptoms of inflammation, including fever, dyspnea, reduced SaO_2, and elevated CRP. This necessity was evaluated from changes in the SHOCS-COVID score, pro-inflammatory biomarkers, and the degree of lung tissue damage without the use of anti-inflammatory drugs; 2) Assess the effective and safe use of colchicine, a well-known, thoroughly investigated, safe, and affordable anti-inflammatory drug.

To address the first objective, the situation in the control group in the end of follow-up with no specific anti-inflammatory therapy should be analyzed. In recent articles, we hypothesized and

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showed that the COVID-19 disease course could rapidly deteriorate due to development of a cytokine storm followed by rapid progression of lung tissue damage, after which it becomes very challenging to save patients who have been admitted to the ICU and put on ventilation [5]. In the control group, patients initially had moderate fever, dyspnea, and reduced SaO_2, a continued decrease in lymphocyte count, an 18-fold increase in CRP, and a significant decrease in LCR to 12.5, which is 8 times lower than the safe level. At the same time, there was a moderate increase in fibrinogen and a more than two-fold increase in D-dimer, i.e., increases in potential indicators of thrombotic complications. The percentage of the lung damage on CT was 26%, which corresponded to grade 2 of the Guidelines of the Russian Ministry of Health. The total score of the clinical condition according to the conventional NEWS-2 score was 4.85, with a score of 5 requiring «critical assessment of the patient's condition whether to be admitted to ICU and receive ventilation». At the beginning of the trial, 54.5% of patients required oxygen support/ventilation. The total severity of the disease according to the original SHOCS-COVID score was 7.71, which corresponds to the moderate or third grade condition.

Symptomatic therapy and the use of anticoagulants and antibiotics proved ineffective in the control patients, and they improved slowly. Their body temperature decreased significantly by 0.48°C, but the decrease in RR by 1 brpm and the increase in SaO_2 by 2% were insignificant. The number of patients with low SaO_2 <94% did not change during two weeks of follow-up. The number of patients requiring oxygen support also remained unchanged and was 50% by the end of follow-up. Moreover, 2 patients who required invasive ventilation stayed at the hospital for 36 and 56 days, respectively, and did not survive despite the subsequent use of GC pulse therapy and anti-cytokine drugs. CRP decreased insignificantly without specific anti-inflammatory therapy and remained more than 4 times higher than the normal upper limit (22.8 mg/dl). An increase in lymphocyte count and LCR, an important indicator of systemic inflammation, was moderate. In the end of follow-up, the LCR was 60.8 and did not reach an adequate level (which is more than 100).

There was no significant improvement in the control group in terms of the risk of COVID-19 thrombotic complications. D-dimer remained increased more than two-fold, fibrinogen was 1.5 times higher than the normal upper limit, NLR also did not change and was 2.79 by the end of follow-up (A value above 3 is associated with an increased risk of thrombosis).

The area of lung damage on CT did not decrease and even tended to increase. By the time of discharge, the median lung tissue damage was 34%, which suggests a slow recovery and development of post-COVID syndrome. Apparently, the lack of timely anti-inflammatory therapy resulted in progression of the disease and failure to achieve a faster recovery.

Thus, in regard to the first objective, it is easy to conclude that clinical management that does not include proactive anti-inflammatory therapy is not effective in treating signs of inflammation, including fever, persistent cough, dyspnea, reduced SaO_2, decreased lymphocyte count. Nor was it effective in decreasing the elevated CRP or in increasing low values of LCR. Thus, the risk of disease progression does not decrease, and the hospital stay is prolonged. This results in higher costs and increased hospital bed usage, which is certainly disadvantageous during the COVID-19 pandemic.

The second objective was to study the efficacy of the proactive anti-inflammatory therapy with colchicine in patients with the novel coronavirus disease. We have previously established the background for the use of colchicine, and we have shown examples of successful treatment using this drug in patients severely ill with COVID-19, coronavirus pneumonia, and inflammation [5]. The publication [17] of the first controlled trial on using colchicine in hospitalized patients with COVID-19, called GRECCO-19, reinforced our enthusiasm for using colchicine. Although that trial failed to show a reliable decrease in CRP as a marker of inflammation, colchicine was significantly superior in clinical endpoints. In the colchicine group, 1/55 patients (1.8%) had negative outcomes (ventilation or death), compared to 7/50 patients (14.0%) in the control group, with OR of 0.11 (95% confidence interval (CI) 0.01–0.96; p=0.046). However, it should be noted that this study included patients without significant lung tissue damage, i.e., at a very early stage of the disease.

At the end of January 2021, the COLCORONA trial was published. This trial studied ambulatory patients with COVID-19 comparable in the severity of the novel coronavirus disease with those in the GRECCO-19 trial. Once again, the medical community was amazed by colchicine's success in treating the novel coronavirus disease [20]. The risk of pneumonia was 2.9% in the colchicine group compared to 4.1% in the placebo group (p=0.02), and the risk of the primary endpoint, death or hospitalization for COVID-19 within 30 days,

was 4.7% in the treatment group versus 5.8% in the control group (OR 0.79; 95.1% CI 0.61–1.03; p=0.08). This means that patients included in the study had the initial stage of the disease. Careful analysis shows that, in the general group of 4,488 patients included in the COLCORONA trial, the reduction of primary endpoint risk was insignificant (p=0.08), although significant differences were observed in the subgroup of 4,159 patients who tested positive by PCR (+), for SARS-CoV-2 RNA (OR 0.75; 95% CI 0.57–0.99; p=0.04). It should be noted that the COLCORONA trial ended early due to logistic issues and to the researchers' desire to provide the findings more quickly to health care systems. An interesting comment was made on these results by Professor Martin Landray of the University of Oxford, the lead researcher of the RECOVERY program, in which the possibility of using colchicine in hospitalized patients with a more severe course of COVID-19 was investigated [25]. Professor Landray said,» We all want to get results as rapidly as possible. But a clear result tomorrow is much more useful than an inconclusive result today.»

The COLCORNA trial examined the possibility of using colchicine before hospitalization, but we pursued a different idea in our trial. The COLORIT program included patients admitted to the hospital with signs of lung damage, who still had signs of inflammation by week 2 according to the criteria discussed above, despite all efforts to reverse the course of disease. Our study's main idea was to try to interrupt the systemic inflammatory process, prevent a cytokine storm by using the proactive colchicine treatment, and, thus, eliminate manifestations of COVID-19 and viral pneumonia.

As we discussed earlier, simple symptomatic treatment, even in combination with anticoagulants and antibiotic therapy, did not allow us to hope for successful outcomes or prevent the need to admit patients to ICU and put them on ventilators. This resulted from fear of a novel and unknown disease that seemed even more intimidating than it was.

We expected colchicine to be effective due to its anti-inflammatory effect, which was fully confirmed in the study. CRP decreased from 99.4 to 4.2 mg/dl (p<0.001), i.e., it was completely normalized and more than 5 times lower than in the control group by the end of week 2 (p=0.014). The lymphocyte count increased significantly, and LCR increased from 14 to 427 (p<0.001), with a safe value being more than 100 [26]. Such pronounced anti-inflammatory effects of colchicine can be explained by the disease substrate, as patients were significantly more severely ill in our study as compared to those who took the drug under the GRECCO-19 and COLCORONA protocols [17, 20].

As a result of colchicine treatment, we observed a rapid improvement in the clinical condition, including a significant decrease in body temperature, reduced dyspnea, and an increase in SaO_2, which increased from 93% to 98% (p<0.001). The number of patients with SaO_2 <94% decreased from 10 (52.6%) to 1 (5.0%), and the number of patients requiring oxygen support/ventilation decreased from 14 (66.7%) to 2 (9.5%) (p<0.001), which by the end of the study was much less than in the control group (p=0.011). The total NEWS-2 score of the clinical condition decreased significantly from the median of 5 «High risk, oxygen support and consult ICU for ventilation» to 1 «Low risk, outpatient treatment» (p<0.001). These results were significantly better than in the control group (p=0.009).

The analysis of risk markers of thrombotic complications, D-dimer and fibrinogen showed that they declined to almost upper normal limit in colchicine group, but these decreases did not reach significance. By the end of the follow-up, fibrinogen in the colchicine group was significantly lower than in the control group (p=0.006). NLR decreased also significantly (p<0.001) in colchicine group. NLR (1.72) was significantly lower than in the control group (p=0.029). The magnitude of this indicator is directly related to the clinical severity of COVID-19 [27], the risk of thrombotic complications [28], which we have shown in the previous trial WAYFARER [6], and even to the area of lung tissue damage on CT [29]. In a recently published analysis, only three factors predicted the risk of the COVID-19 disease progression: age, NLR, and lung damage on CT [30].

By the end of week 2, the lung damage area (13%) was significantly smaller than in the control group (34%, p=0.041). It is well-known that improvements on CT may lag the clinical manifestations, and we may not have had enough follow-up time to observe more significant changes [31, 32]. Moreover, there is no single point of view on the time of complete normalization of COVID pneumonia on lung CT, but it is assumed to be no earlier than in 4 weeks after discharge from the hospital [33]. There was weak, but significant, correlation between changes in lung tissue damage on CT and the indicator of inflammation, LCR (r=–0.37, p=0.025). Perhaps a relatively low correlation can be explained by the dissociation between the time for reducing inflammation and lung tissue damage on CT.

We used our original integrated SCOCS-COVID score, a reflection of the clinical status, need for

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and type of oxygen support, inflammation marker CRP, thromboembolic marker D-dimer andlung tissue damage on CT as the primary endpoint of the study [1]. This score has been successfully used to evaluate the treatment results in patients with COVID-19 in trials with GCs (WAYFARER) [6], bromhexine and spironolactone (BISCUIT) [4], and hydroxychloroquine [34].

In our study, the use of colchicine was accompanied by a pronounced and significant decrease in the SHOCS-COVID score from 8 to 2 (median values, $p<0.001$), which corresponds to the improvement from stage 3 (moderate severity) to stage 1 (mild severity). The post-treatment differences between the SHOCS-COVID scores in the colchicine and control groups were significant. The median score was 7 in the control group, i.e., moderate severity of the disease, $p=0.002$. Patients spent less time in the hospital, and there was no critical deterioration or death. We conducted a correlation analysis between changes in the SHOCS-COVID score and changes in other parameters that reflected the real severity of the patient's condition in COVID-19. In this regard, we wish to remind the reader of two underestimated, simple, and accessible indicators: lymphocyte count (correlation of the delta with the SHOCS-COVID delta, $r= -0.59$, $p=0.0004$) and NLR (correlation of the delta with the SHOCS-COVID delta, $r=0.59$, $p=0.0004$).

Conclusion

Based on our trial, we conclude that colchicine 1 mg for 1–3 days followed by 0.5 mg/day for 14 days is effective as a proactive anti-inflammatory therapy in hospitalized patients with COVID-19 and viral pneumonia. Our study shows a potential for preventing progression of the disease by proactive, anti-inflammatory therapy. The management of such patients without proactive anti-inflammatory therapy is likely to be unreasonable and may worsen the COVID-19 course. However, the findings should be treated with caution, given the small size of the study.

The COLORIT program contributes further to understanding the appropriateness of using colchicine in the treatment of COVID-19, as well as do the published data of the GRECCO-19 and the COLCORONA trials and the much-anticipated RECOVERY trial. All trials included a somewhat different group of patients, which only expands the understanding of the possibility of early, and yet varying in time, use of colchicine to stop the progression of the novel coronavirus disease.

Additional materials

Boxplot graphs with the dynamics of SHOCS-COVID, NEWS-2, SPO_2 and others are available in the section «Additional materials» to the article on the website of the journal.

Limitations of this study

No appropriate randomization, few patients.

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