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How evaluate results of treatment in patients with COVID-19. Symptomatic Hospital and Outpatient Clinical Scale for COVID-19 (SHOCS–COVID)

Aim	Development of a novel scale for assessing medical state in patients with new coronavirus infection based on clinical and laboratory disease severity's markers, named SHOKS-COVID scale.
Material and Methods	Clinical Assessment Scale (SHOKS-COVID) is based on 1: clinical parameters (respiratory rate, Body temperature, SpO_2 need and type of ventilation support) 2: Inflammation markers (C reactive protein (CRP) and prothrombotic marker (D-dimer)) and 3: percent of lungs injury by CT. This scale was used in several clinical studies in patients with varying severity of the course of the COVID 19. SHOKS-COVID scale was also compared against some additional biomarkers and with length of hospital stay.
Results	In patients with severe COVID-19 (Clinical Trial WAYFARER – 34 patients), SHOKS-COVID scores were correlated with the degree of inflammation: CRP (r=0.64; p<0.0001); the ratio lymphocytes/CRP (r= –0.64; p<0.0001). Also, SHOKS-COVID score correlated with the D-dimer (r=0.35; p<0.0001) and percentage lung damage on multispiral computed tomography (MSCT) – (r=0.77, p<0.0001) and length stay in the clinic (r=0.57, p=0.0009). In patients with mild course (BISQUIT Study – 103 patients), SHOKS-COVID scores had a statistically significant positive correlation with length of fever (r=0.37; p=0.0002) and length of stay in the clinic (r=0.52, p<0.0001) and negatively correlated with the ratio of lymphocytes/CRP (–0.78, p<0.0001) and the level of CRP (r=0.78; p<0.0001). Patents were grouped based on severity of COVID 19 and median and interquartile range (IQR) of SHOCKS-COVID were measured in these groups. Median and IQR of SHOCKS-COVID were 2.00 [1.0–2.5] points in mild course, 4.0 points [3.0–5.0] in moderate course, 7.0 points [6.0–9.0] in moderately severe course,12.0 points [10.0–14.0] in severe course of disease and 15.0 points [14.5–15.5] in extremely severe patients.
Conclusion	Here we report a novel scale of COVID 19 disease progression. This scale ranges from zero in asymptomatic patients (with normal range of biomarkers and without lung damage on CT) to fifteen in extremely severe patients. The scores for SHOKS-COVID are increasing, in parallel with the deterioration of all other biomarkers of severity and prognosis in patients with new coronavirus infection. Based on the analysis carried out, we were able to determine values of SHOKS-COVID scale and levels of main clinical and laboratory markers in patients with different severity of COVID-19.

Keywords	COVID-19; SHOKS-COVID; risk score
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The novel coronavirus pandemic caused by SARS-CoV-2, which has already affected more than 43 million people and led to more than 1.2 million deaths, requires effective treatments. This is relevant concerning both the most severe forms of the disease accompanied by viral pneumonia with the total involvement of bronchioles and alveoli, vasculitis and thrombosis of small pulmonary vessels, requiring mechanical ventilation of the lungs, and the initial stage of the disease when the main issue seems to be reducing the viral load.

Thousands of trials, most of which are observational and non-randomized trials, are published instantly (most often before being reviewed) not to «overlook gold grain in the rock» and allow possible researchers to immediately share their considerations. Therefore, it is useful to have some more or less objective tool to

Table 1. The WHO recommendations on COVID-19 trial endpoints

Uninfected	No clinical and virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized, mild disease	No oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized, severe disease	Noninvasive ventilation	5
	Intubation, invasive ventilation	6
	Ventilation + ECMO, dialysis, inotropes, etc.	7
Dead	Death	8

ECMO, extracorporeal membrane oxygenation.

evaluate the data obtained in the trials, if only to make the results of the different protocols comparable.

The composite endpoint of death and transferring to an intensive care unit and placing on mechanical ventilation is used to analyze the most severe patients like, for example, with another potentially fatal disease, chronic heart failure (CHF). Even so, it is ambiguous whether to transfer to the ICU or order mechanical ventilation. Is placing on mechanical ventilation completely standardized? How should patients, whom we were ready to place on invasive ventilation but did not have that option, be taken into account? How not to forget that most intensivists become more flexible about the mandatory mechanical ventilation by this October.

And what about patients at earlier stages of the disease whose treatment outcomes improved significantly. This spring, the mean mortality rate was about 7%, twice as high in some countries and especially in older patients. The mean mortality rate is currently not higher than 2.5%, and hundreds and thousands of patients should be included in the trial to use it as the endpoint. We by no means disagree with the WHO's original 8-point clinical improvement score, but it covers only the disease outcomes (Table 1) [1].

Secondary endpoints should have included evaluating patients' clinical condition, the severity of the disease (including duration and severity of symptoms and fever), and estimation of viremia in biological materials. This is not standardized either. Some of the published results did not clearly indicate what «stabilization» or reduction of cough meant [2]. Moreover, according to the WHO experts, it is necessary to assess the need to transfer patients to the ICU and place on mechanical ventilation and the need for inotropes, dialysis, extracorporeal membrane oxygenation (ECMO), which is also not always objective, as we have discussed above. Clinical status (mortality) is planned to be evaluated by day 28, which is also controversial, given that some patients were ventilated for more than a month. When federal centers treating patients with the novel coronavirus infection were closed urgently by a decision of the Ministry of Health of the Russian Federation, including the University Clinic of Moscow State University, we had only four lethal outcomes. However, seven ventilated patients were transferred to other facilities. Some of them died, and how should we take these statistics into account?

The endpoints used to evaluate the efficacy of antiviral therapy at earlier stages of the disease were the number of days to temperature normalization and the elimination of clinical symptoms by the end of the course (5, 10, 14 days) of drugs reducing viral load, which is also not standardized. In some cases, the short course of treatment was more effective than the long-term treatment [3].

Given that clinical symptoms are included in any system of evaluation of the novel coronavirus disease course and treatment efficacy, and thus requires formalization, an attempt was made to adapt the NEWS2 score for this purpose (Table 2), which was used initially to assess the severity of distress syndrome [4].

The NEWS2 score was developed to evaluate the severity of patients with acute respiratory syndromes and is aimed mainly at assessing the current patient's condition and less at evaluating the disease prognosis. Classic clinical manifestations, such as respiratory rate (RR), oxygen blood saturation, need for ventilation, state of consciousness, body temperature, heart rate (HR), and systolic blood pressure (SBP), were used as a basis especially for routing of patients. At the beginning of the COVID-19 pandemic, this was a very urgent task, and an incorrect assessment of the patient's prognosis caused intensive care units to become overloaded.

This score can be calculated using a special online calculator [5], although it is not difficult to calculate it from the table. 0–4 – low risk, treatment in the ward; 3 for any indicator – moderate risk, treatment in the ward, oxygen by mask; 5–6 – high risk, treatment in the ward,

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oxygen by mask, consultation with ICU; 7–8 – very high risk, treatment in ICU.

At the beginning of the pandemic, it became clear that the NEWS2 distress syndrome severity score should be modified for patients with COVID-19. The Chinese researchers supplemented this score with the age parameter and added the maximum number of points (3) for the age of over 65 years [6]. That modification reflected an early understanding of the COVID-19 course during the Wuhan outbreak. It is evident now that age is not the only aggravating factor. Concomitant diseases also worsen prognosis. The maximum risk is observed in the subgroup of patients over 80 years old, which is 6 times higher than in patients aged 65 [7].

In the modified NEWS2 score, low risk corresponds to 0, average risk is 1–4 (to be admitted to a common ward), high risk – 5–6 (treatment in the ward, noninvasive ventilation, consultation with ICU), and very high risk – 7 or more (transfer to ICU).

The evaluation of the condition of patients with COVID-19 depends on several key parameters but not only the severity of dyspnea, oxygen blood saturation, and the need for lung ventilation. These parameters characterize more the severity of pulmonary involvement and respiratory failure. The state of consciousness is directly correlated with transferring to the ICU and especially placing on mechanical ventilation.

We tried to supplement this score with some clinical and laboratory indicators directly correlated with the prognosis for patients with COVID-19.

The percentage of pulmonary tissue damage on CT is one of the main indicators. However, it is not always correlated with clinical signs of air shortage but can negatively affect the prognosis.

Progressive systemic inflammation accompanied by decreased lymphocyte count and the elevated neutrophil count is an essential element of the pathogenesis of COVID-19, as is the degree of the inflammatory process, the main markers of which are the severity of fever and the C-reactive protein (CRP) levels. Uncontrolled activation of immune cells by cytokines in the inflammation site and release of more cytokines and chemokines is called a cytokine storm, which increases the risk of acute respiratory distress syndrome (ARDS) and can cause polyorgan failure. Thus, a significantly elevated CRP level is an ominous harbinger of adverse prognosis.

The most dangerous manifestation of the novel coronavirus disease is an increased risk of thrombotic and thromboembolic complications typical of COVID-19 and may cause multiple organ failure and worsen the prognosis [8]. Several trials have shown that COVID-19 can be accompanied by hypercoagulation with inhibition of fibrinolysis, which leads to microthrombosis in the lung, kidney, and heart vessels, and an increased risk of venous thromboembolism (VTE), including pulmonary embolism (PE), and arterial thromboembolism, including the development of stroke [9, 10]. Elevated D-dimer, a fibrin degradation product used as a marker of increased risk of thrombosis, was used in several trials as an independent factor of the poor prognosis for patients with the novel coronavirus infection also selected to create a new integral severity score [9]. Based on the successful experience of developing a similar integral score, Symptomatic Hospital and Outpatient Clinical Score (SHOCS) for patients with chronic heart failure (Belenkov Y. N. and Mareev V. Y., 2000), we sought to create a similar score to evaluate the clinical condition of patients with the novel coronavirus disease.

The objective of our work was to develop an original score to assess the clinical condition of patients with coronavirus disease, taking into account the main markers of the disease severity, SHOCS-COVID.

Material and Methods

Table 3 presents the original SHOCS-COVID score that takes into account the main markers of the disease severity.

Table 2. National Early Warning Score 2 (NEWS2)

Parameters	Score						
	3	2	1	0	1	2	3
RR, breaths per min	<8		9–11	12–20	–	21–24	> 5
SaO_2, %	<91	92–93	94–95	>96	–	–	–
Oxygen	–	O_2 ventilation, FiO_2>21	–	Air, FiO_2=21	–	–	–
SBP, mm Hg	<90	91–100	101–110	111–219	–	–	>220
HR, bpm	<40	–	41–50	51–90	91–110	111–130	>131
Consciousness	–	–	–	Clear	–	–	Altered
Body temperature, °C	<35	–	35,1–36	36,1–38	38,1–39	>39	–

RR, respiratory rate; SaO_2, oxygen saturation; SBP, systolic blood pressure; RR, respiratory rate.

We speculated that the score 0 to 3 corresponds to the low risk, 4–6 to the medium risk, 7–10 to the average risk, 11–14 to the high risk, and finally the score of 15 or higher corresponds to the extremely high risk of the unfavorable course of the disease, rapid progression of pulmonary involvement, multiple organ failure, which are extremely difficult to treat.

We used this score for the first time in the WAYFARER trial (n=34), which studied the possibility of treating patients with severe bilateral viral pneumonia, activation of the inflammatory autoimmune element of the disease pathogenesis, and the onset of the cytokine storm. The primary endpoint of the trial was the changes in the SHOCS-COVID score, which entirely confirmed the efficacy of glucocorticoids (GCs) in patients with the coronavirus infection [10]. To test and validate the SHOCS-COVID score, we used it in the BISCUIT trial (n=103) to evaluate the efficacy of treatment in patients with initial and moderate manifestations of the novel coronavirus disease [11, 12].

Results

Figure 1 shows the correlations between the SHOCS-COVID scores and the main indicators of severity in patients with coronavirus pneumonia and cytokine storm according to the WAYFARER trial.

As shown in the figure, the SHOCS-COVID score was closely correlated with the degree of inflammation in patients with severe COVID-19: CRP (r=0.64; p<0.0001) and one of the most informative criteria for the decompensation and the onset of the cytokine storm, lymphocyte-to-CRP ratio (r= –0.64; p<0.0001). At the same time, there was also a correlation with the D-dimer level (r=0.35; p<0.0043), which predicts the risk of thrombotic and thromboembolic complications. Finally, there was a close relationship between the degree of lung damage on MSCT, the SHOCS-COVID scores, and the duration of hospital stay (r=0.57, p=0.0009). Thus, this score is a reliable tool to assess the severity of patients with severe novel coronavirus disease.

In the BISCUIT trial, significant changes in the SHOCS-COVID score corresponded to the improvement of the disease course in both the bromhexine/spironolactone group and the control group. In a less severe course of the disease, we could not identify differences between the groups, which does not reduce the informative value of the integral method of evaluating the severity of the COVID-19 course. During the treatment with bromhexine and spironolactone, a faster temperature normalization and a trend towards shorter stay in hospital were observed. Therefore, we performed a correlation analysis to find a correlation between

Table 3. Symptomatic Hospital and Outpatient Clinical score for COVID-19 (SHOCS-COVID). 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, °C	35.5–37	0
		37.1–38.5	1
		>38.5	2
3.	SaO_2, %	>93	0
		90–92.9	1
		<90	2
4.	Ventilation	Not needed	0
		Low-flow ventilation in room air	1
		Noninvasive, mechanical ventilation in the ICU	2
		Invasive, mechanical ventilation in the ICU	3
5.	CRP, 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.	MSCT, % of pulmonary lesions	No pneumonia	0
		0–24	1
		25–49	2
		50–74	3
		75–100	4
	TOTAL	**MAXIMUM**	**20**

RR, respiratory rate; SaO2, oxygen saturation;
CRP, C-reactive protein; MSCT, multislice computed tomography.

Table 4. Correlation analysis of the main indicators and the number of days to temperature normalization. BISCUIT trial

Parameter	Days to temperature normalization, n	Significance (p)
CRP, mg/dL	0.45	>0.0001
LCR	-0.43	0.0001
SHOCS-COVID, score	0.37	0.0002
D-dimer, μg/mL	0.35	0.0004
Age, years	0.26	0.0101
% of lung damage on MSCT	0.24	0.0199

CRP, C-reactive protein; LCR, lymphocyte-to-CRP ratio;
MSCT, multislice computed tomography.

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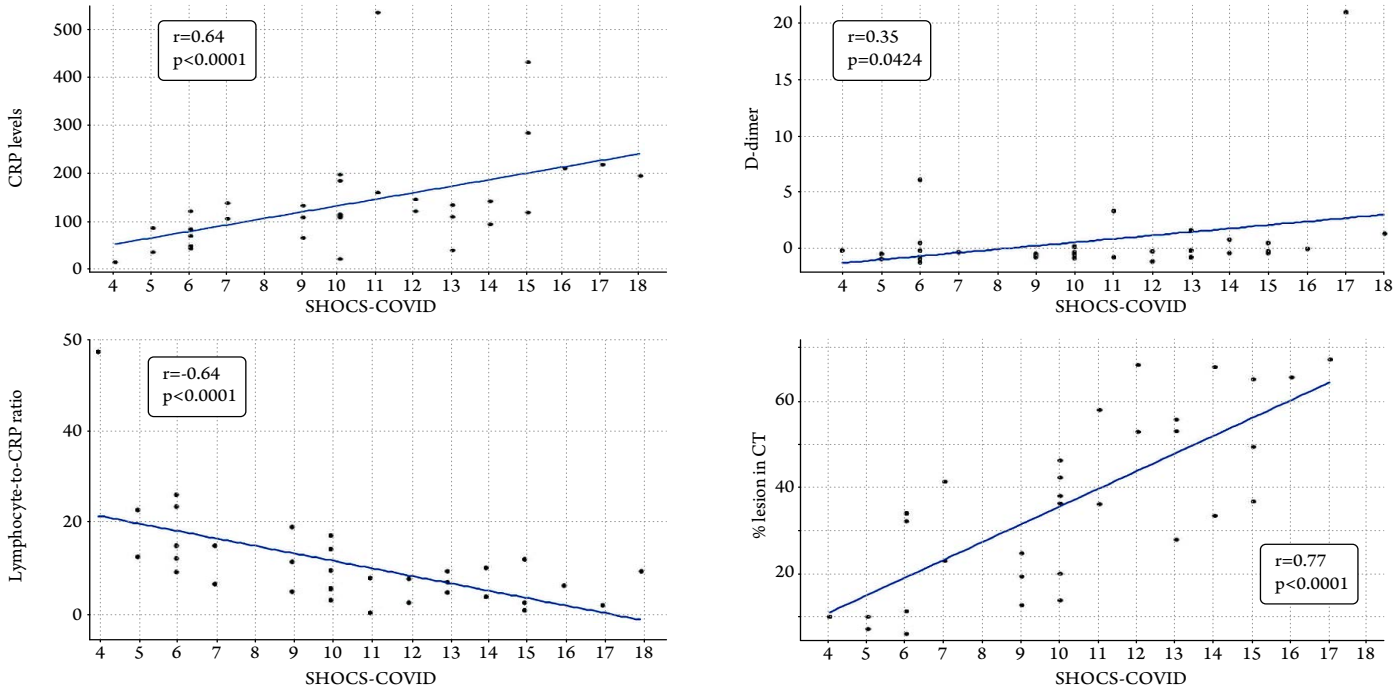
Figure 1. Correlation between the CHOKS-COVID scores and inflammation markers (CRP and lymphocyte-to-CRP ratio), thrombosis (D-dimer), and percentage of lung damage on MSCT. WAYFARER trial



the indicators of interest, especially the SHOCS-COVID score, with the number of days to temperature normalization and the number of days in hospital.

As shown in Table 4, the SHOCS-COVID scores in this study were statistically significantly correlated with the number of days with elevated temperature (r=0.37; p=0.0002), second only to the CRP levels and the lymphocyte-to-CRP ratio, and superior in correlation significance to D-dimer, age, and the percentage of lung damage on MSCT. The SHOCS-COVID scores were closely correlated with the number of days patients spent in hospital (r=0.51, p<0.0001, which is the closest correlation among all the indicators of interest). Then LCR (r=–0.78; p<0.0001) and CRP (r=0.78; p<0.0001)

Figure 2. Correlation between the SHOCS-COVID scores, days of hospital stay, lung damage, and clotting marker (neutrophil-to-lymphocyte index)

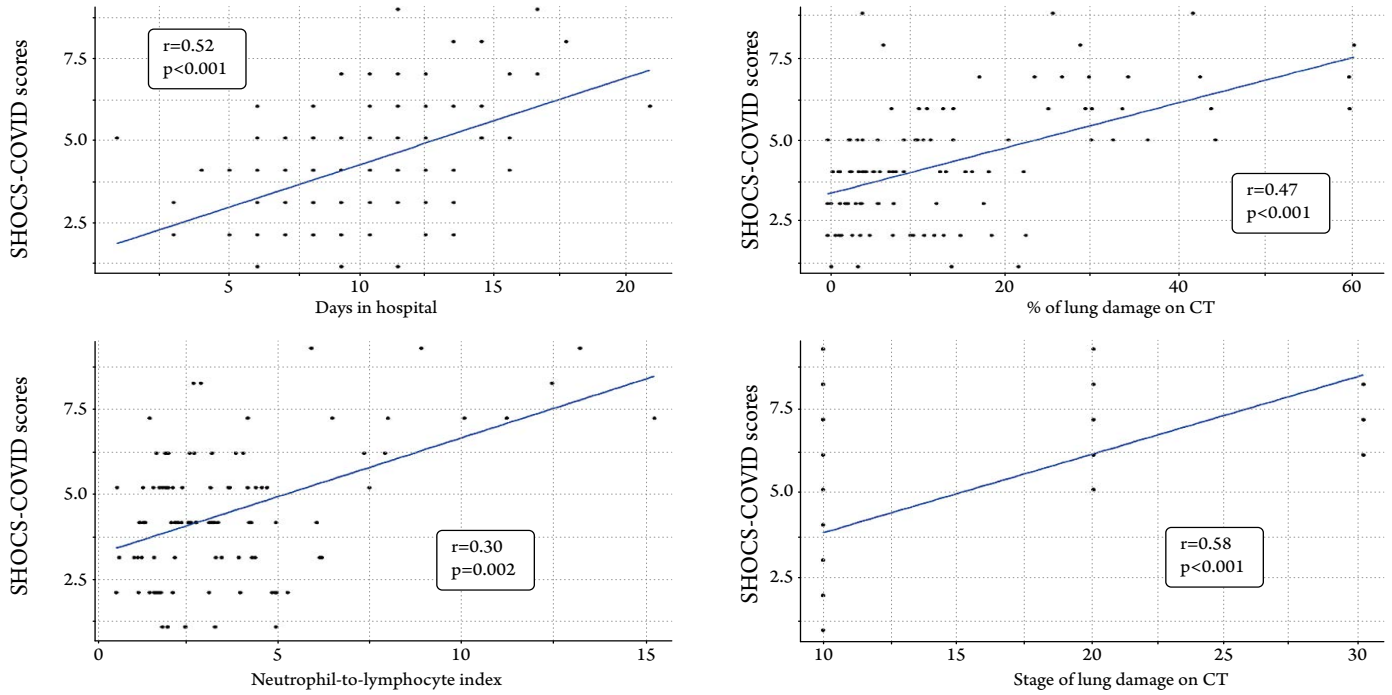


Figure 3. Correlation between the SHOCS-COVID scores, days to temperature normalization, decreased lymphocyte count, and inflammation markers (CRP and lymphocyte-to-CRP ratio)

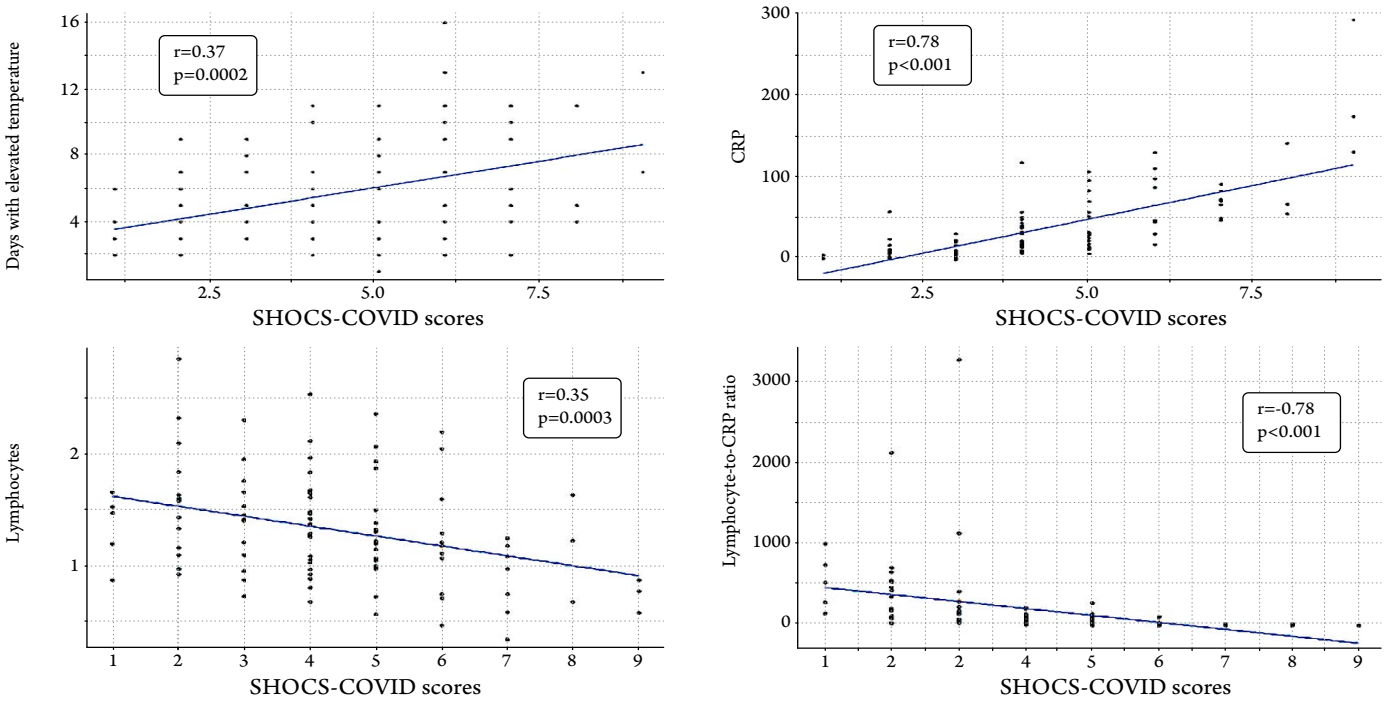


Table 5. SHOCS-COVID scores depending on the severity of the novel coronavirus disease compared to other common characteristics

Course of the disease	SHOCS-COVID	CRP, mg/dL	D-dimer, μg/mL	Lymphocytes, 109/L	CT, %	LCR	NLR
Mild	2.00 [1.0 – 2.5]	9.75 [4.89; 17.5]	0.25 [0.14; 0.43]	1.47 (0.53)	5.90 [2.80; 12.2]	148 [77.3; 360]	2.29 [1.55; 4.11]
Moderate-to-severe	4.00 [3.0 – 5.0]	39.8 [20.6; 65.2]	0.44 [0.32; 0.52]	1.16 (0.47)	10.8 [6.85; 15.1]	35.8 [14.3; 55.9]	3.51 [2.53; 6.38]
Moderate	7.00 [6.0 – 9.0]	95.1 [67.0; 134]	1.15 [1.00; 1.36]	1.05 (0.59)	25.6 [12.6; 34.7]	12.2 [9.32; 19.2]	4.06 [2.12; 5.45]
Severe	12.0 [10.0 – 14.0]	134 [112; 194]	1.41 [1.20; 1.96]	0.66 (0.41)	53.2 [37.3; 65.1]	6.32 [3.94; 9.47]	6.05 [3.8; 11.2]
Extremely severe	15.0 [14.5 – 15.5]	209 [119; 281]	1.41 [1.33; 1.53]	0.86 (0.51)	53.2 [49.7; 64.9]	6.32 [2.70; 7.05]	6.80 [3.80; 11.2]

All indicators other than lymphocyte level are expressed as the median and the 25th and 75th percentiles.
The mean and standard deviation are given for the lymphocyte levels.

followed. This allows positively evaluating the significance and adequacy of the SHOCS-COVID score calculation method to determine the clinical condition and the prognosis for patients with different severity of the disease.

Figures 2 and 3 show the correlations between the SHOCS-COVID scores and the main indicators of the severity at the early stages of COVID-19.

As seen in Figure 2, the duration of stay in hospital directly correlated with the SHOCS-COVID score and the degree of lung damage on CT (both percentage r=0.47, p<0.001, and the grades according to the guidelines of the Russian Ministry of Health: r=0.58, p<0.001). The correlation between the SHOCS-COVID score and the clotting risk (neutrophil-to-lymphocytes ratio) was significant (r=0.30, p=0.002), but less close than at the more severe stage of the disease. However, our findings confirm one more time that thromboprophylaxis is reasonable even at the initial stages of COVID-19.

Figure 3 shows a significant direct correlation of the SHOCS-COVID score with the number of days to temperature normalization (r=0.37, p=0.0002) and indirect correlation with lymphocyte count (r=–0.35, p=0.0003), which is indicative of the acute phase of the disease.

Discussion

In our opinion, the close correlation of the integral clinical score with the parameters of systemic inflammation: direct correlation with CRP (r=0.78, p<0.001) and inverse

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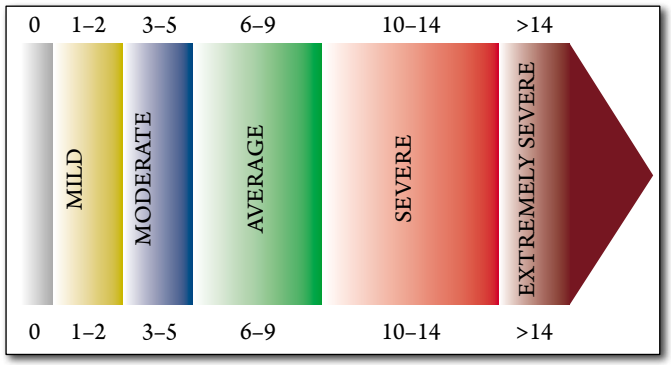
Figure 4. COVID-19 severity according to the SHOCS-COVID score



correlation with LCR (r= –0.78, p<0.0001) according to the BISCUIT trial, is of great interest.

This reinforces the risk of progressive inflammation even in patients at the initial stage of the disease and minimal lung damage on CT. This confirms the idea of early proactive therapy to prevent the progression of the novel coronavirus disease. Based on the examinations performed, we determined the ACTUAL SHOCS-COVID scores corresponding to different severity of the disease (Table 5).

The score increases as do all other markers of the disease severity and the prognosis of patients with the novel coronavirus disease, from the asymptomatic course (normal biomarker levels and no lesion on CT=0) to the most severe forms of the disease requiring transfer to the ICU.

Below is the SHOCS-COVID score in a convenient form for practical use (Figure 4).

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REFERENCES

1. World Health Organisation. COVID-19 Therapeutic Trial Synopsis. [Av. at: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf]. 2020.
2. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. 2020. [Av. at: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v4] DOI: 10.1101/2020.03.17.20037432.
3. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. New England Journal of Medicine. 2020; NEJMoa2015301. [Epub ahead of print]. DOI: 10.1056/NEJMoa2015301
4. Royal College of Physicians. National Early Warning Score (NEWS) 2. [Av. at: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2]. 2017.
5. MediCalc. National Early Warning Score 2. [Internet] Available at: http://www.scymed.com/en/smnxpw/pwfhc210.htm
6. Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019–2020 epidemic: preparing intensive care units – the experience in Sichuan Province, China. Intensive Care Medicine. 2020;46(2):357–60. DOI: 10.1007/s00134-020-05954-2
7. The OpenSAFELY Collaborative, Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. Epidemiology. 2020. [Av. at: http://medrxiv.org/lookup/doi/10.1101/2020.05.06.20092999.] DOI: 10.1101/2020.05.06.20092999.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62. DOI: 10.1016/S0140-6736(20)30566-3
9. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. Journal of Thrombosis and Haemostasis. 2020;18(6):1324–9. DOI: 10.1111/jth.14859
10. Mareev V.Yu., Orlova Ya.A., Pavlikova E.P., Matskeplishvili S.T., Krasnova T.N., Malahov P.S. et al. Steroid pulse -therapy in patients With coronAvirus Pneumonia (COVID-19), sYstemic inFlammation And Risk of vEnous thRombosis and thromboembolism (WAYFARER Study). Kardiologiia. 2020;60(6):15–29. [Russian: Мареев В.Ю., Орлова Я.А., Павликова Е.П., Мацкеплишвили С.Т., Краснова Т.Н., Малахов П.С. и др. ПУльс-Терапия стероидными гормоНамИ больных с Коронавирусной пневмонией (COVID-19), системным воспалением и риском венозных тромбозов и тромбоэмболий (исследование ПУТНИК). Кардиология. 2020;60(6):15-29]. DOI: 10.18087/cardio.2020.6.n1226
11. Mareev V.Yu., Orlova Ya.A., Pavlikova E.P., Matskeplishvili S.T., Akopyan Zh.A., Plisyk A.G. et al. Combination therapy at an early stage of the novel coronavirus infection (COVID-19). Case series and design of the clinical trial "BromhexIne and Spironolactone for CoronavirUs Infection requiring hospiTalization (BISCUIT)". Kardiologiia. 2020;60(8):4–15. [Russian: Мареев В.Ю., Орлова Я.А., Павликова Е.П., Мацкеплишвили С.Т., Акопян Ж.А., Плисюк А.Г. и др. Возможности комбинированной терапии на раннем этапе течения новой коронавирусной инфекции (COVID-19). Разбор клинических случаев и дизайн исследования: Бромгексин И Спиронолактон для лечения КоронаВирусной Инфекции, Требующей госпитализации (БИСКВИТ). Кардиология. 2020;60(8):4–15]. DOI: 10.18087/cardio.2020.8.n1307
12. Mareev V.Yu., Orlova Ya.A., Plisyk A.G., Pavlikova E.P., Matskeplishvili S.T., Akopyan Zh.A. et al. Results of an open prospective controlled comparative study on the treatment of new coronavirus infection (COVID-19): Bromhexine and spironolactone for the treatment of coronavirus Infection requiring hospitalization (BISCUIT). Kardiologiia. 2020;60(11). [Russian: Мареев В.Ю., Орлова Я.А., Плисюк А.Г., Павликова Е.П., Мацкеплишвили С.Т., Акопян Ж.А. и др. Результаты открытого проспективного контролируемого сравнительного исследования по лечению новой коронавирусной инфекции (COVID-19): Бромгексин И Спиронолактон для лечения КоронаВирусной Инфекции, Требующей госпитализации (БИСКВИТ). Кардиология. 2020;60(11)]. DOI: 10.18087/cardio.2020.11.1440