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ИНФОРМАЦИЯ ПРОТИВ ПАНДЕМИИ
COVID-19
INFORMATION AGAINST PANDEMIC

Moscow
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2022

ФОНД ПРЕЗИДЕНТСКИХ ГРАНТОВ

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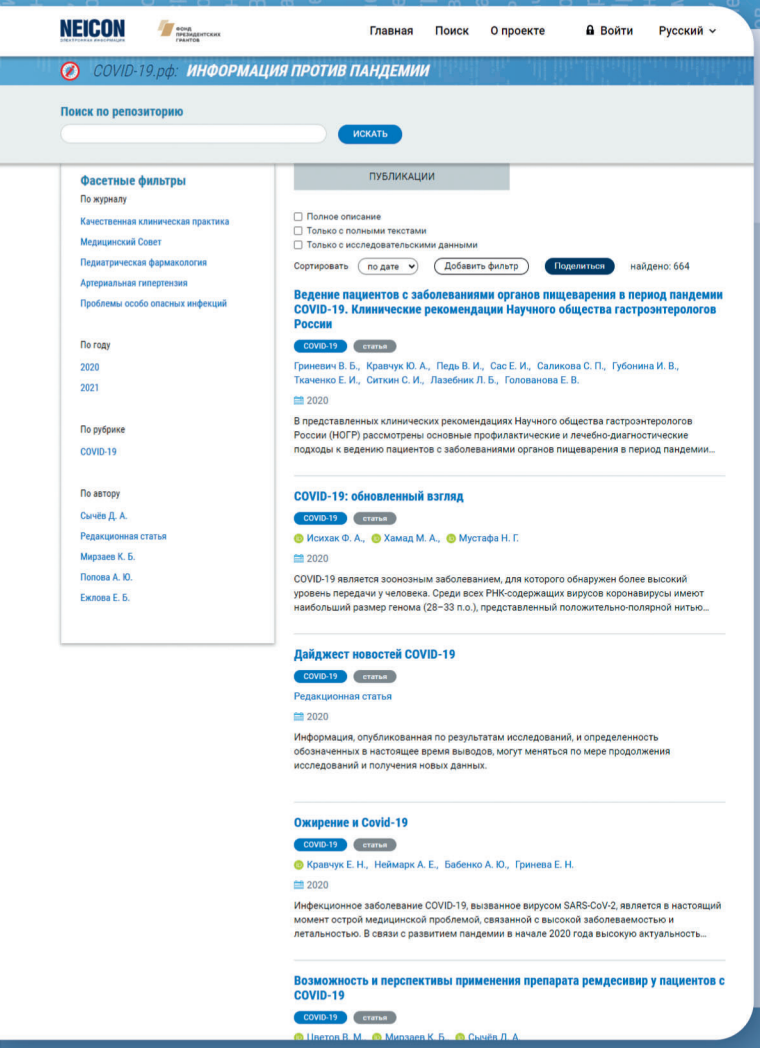

Цель проекта:

Обеспечение легального открытого доступа к российскому сегменту научной информации о COVID-19.

Задачи:

- Разработка программного обеспечения для создания коллекции COVID-19.рф: информация против пандемии
- Наполнение коллекции COVID-ресурсами проекта «Открытая наука России» и ресурсами платформ elpub.ru и preprints.ru: журнальными статьями и препринтами
- Масштабирование коллекции за счет использования международных наукометрических баз данных (МНБД)
- Продвижение проекта и обучение пользователей
- Интеграция российского проекта в мировое информационное пространство по коронавирусам с тегом #COVID-19
- Целевая аудитория: лица, участвующие в борьбе с пандемией COVID-19, и лица, пострадавшие от коронавирусной инфекции и испытывающие проблемы доступа к достоверной информации о COVID-19 в условиях «инфодемии» — распространения недостоверной информации

Приглашаем всех заинтересованных лиц подписать Декларацию об объединении усилий научного сообщества в борьбе с COVID-19 и присоединиться к проекту «COVID-19.рф: информация против пандемии» https://covid19.neicon.ru/

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Nosocomial Infection in Patients with Severe and Critical COVID-19

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Нозокомиальная инфекция у пациентов с тяжелым и крайне тяжелым течением COVID-19

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Summary

The aim of the study was to determine the etiology and frequency of nosocomial infections in patients with severe and critical COVID-19.

Material and methods. A retrospective, single-center study included 168 patients with COVID-19 admitted to the intensive care unit (ICU). All episodes of infection, clinical and laboratory characteristics, and outcome were documented in patients.

Results. Hospital-acquired infections were detected in 82 (48.8%) of 168 patients, more frequently in men (P=0.028). A total of 232 episodes of nosocomial infections were observed including ventilator-associated pneumonia (48.2%), bloodstream infection (39.2%), nosocomial pneumonia/tracheobronchitis (13.4%), and urinary tract infection (5.2%). The main causative agents of nosocomial infections were resistant strains of Acinetobacter baumannii and Klebsiella pneumoniae. Infections developed on the average on day 6 [3; 9] of ICU stay and were associated with the initial severity of the patients assessed by SOFA (P=0.016), SpO_2 (P=0.005), lymphopenia severity (P=0.003), Neutrophil-Lymphocyte Ratio (P=0.004), C-reactive protein (P=0.01), aspartate aminotransferase (AST) level (P=0.022), or vitamin D (P=0.035) levels. Patients diagnosed with infection were more likely than those without infections to require mechanical ventilation (67.6% vs 32.4%, P<0.001), high-flow oxygen therapy (50.0% vs 31.0%, P=0.020), renal replacement therapy (36.8% vs 9.3%, P=0.003), and had longer ICU length of stay (13 [9; 18] vs 4 [2; 8], P<0.001), hospital length of stay (19 [14; 29] vs 15 [11; 20], P=0.001) and mortality (47 (57.3%) vs 25 (29.0%), P<0.001).

Conclusion. In patients with severe and critical COVID-19 a high incidence of nosocomial infections was found, which negatively affected the outcome. In more than half of the cases, the infection was caused by resistant strains of Gram-negative bacilli. Procalcitonin is a useful biomarker for identifying bacterial infection in patients with COVID-19.

Keywords: COVID-19; SARS-CoV-2; nosocomial infection; intensive care; outcome

Conflict of interest. The authors declare no conflict of interest.

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Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains a major social and financial burden. It posed multiple challenging questions to the medical community in general and intensive care unit (ICU) specialists in particular. One of the major issues associated with SARS-CoV-2 infection is that a significant proportion of coronavirus disease 2019 (COVID-19) patients suffer from respiratory failure requiring intensive care [1, 2].

The development of immune hyperinflammatory response associated with COVID-19 has prompted the widespread use of immunomodulatory drugs [3], which began long before the evidence of their efficacy has been unequivocally established in large clinical trials due to the emergency of the pandemic situation. These drugs included glucocorticosteroids and numerous monoclonal antibodies including tocilizumab and olokizumab.

Despite the improved outcome with the use of above-mentioned drugs, COVID-19 patients have an increased risk of developing a secondary bacterial infection [4, 5]. In patients with moderate disease, superinfection frequency was reported to range from 3.6% to 24% [6, 7], whereas very limited data are currently available for COVID-19 patients admitted to ICU.

This study aimed to determine the etiology and frequency of nosocomial infections in patients with severe and critical COVID-19.

Materials and Methods

This retrospective single-center study included 168 patients with severe and critical COVID-19, who were hospitalized in the ICU of Federal Scientific and Clinical Center of Specialized Types of Medical Care and Medical Technologies of the Federal Medical and Biological Agency of Russia from April 6 to July 1, 2020. During this period, the clinical center served as an infectious disease hospital for patients with COVID-19. The diagnosis of COVID-19, assessment of disease severity, and patient therapy were done according to the temporary guidelines of the Ministry of Health of the Russian Federation on prevention, diagnosis and treatment of novel coronavirus infection (COVID-19) [8]. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the local ethical committee of the Federal Scientific and Clinical Center (Protocol No. 5, June 3, 2020).

The following information was collected from the study participants: demographics, comorbidities, routine laboratory tests (complete blood count, common urine analysis, blood clinical chemistry, coagulation test), Sequential Organ Failure Assessment (SOFA) score, localization and causative agent of infection, as well as clinical outcome. Only laboratory-confirmed nosocomial infection cases with a positive culture with a titer above the diagnostic cut-off were included in the study. These patients were also required to have a clinical presentation of the infection and/or worsening organ function [9]. Microorganisms were considered multidrug-resistant if they were resistant to more than one antibiotic drug from at least 3 groups of antibacterial drugs [10].

Statistical analysis.

Quantitative data are presented as the median (*Me*) and interquartile range [25%; 75%], category parameters are shown as absolute numbers (n) and percentage (%). Given that most of the quantitative data were not normally distributed, a non-parametric significance test, such as the Mann–Whitney test, was used for the analysis. For categorical parameters, chi-square statistics with Yates correction, and Fisher's exact test were used. The proportion of missing data did not exceed 10% for each parameter. The differences were considered significant if *P*-value was below 0.05. The SPSS 28.0.0.0 (IBM SPSS Statistics, Chicago, IL, USA) software package was used for data processing and statistics.

Results

Nosocomial infection was detected in 82 (48.8%) out of 168 patients. Clinical characteristics of the patients are shown in Table 1 which compares patients who developed a superinfection with those who did not. Groups of COVID-19 patients with or without superinfection were very similar in their age, however, inter-group differences in terms of gender and disease severity (SOFA scores and SpO_2) were notable (Table 1). Respiratory failure was the most common cause of admission to the ICU.

Hypertension, coronary heart disease, and diabetes mellitus were the most frequent comorbidities in the patients of both groups. No significant differences in the incidence of these diseases between the groups were observed. Patients in the superinfection group, in contrast to the control group, needed norepinephrine (76.8% и 31.3%, $P<0.001$), mechanical ventilation (67.6% vs 32.4%, $P<0.001$), high-flow oxygen therapy (50% vs 31%, $P=0.033$) more often. Also, superinfection group patients were more likely to receive renal replacement therapy (36.8% vs 9.3%, $P=0.001$) even though fewer patients had chronic kidney disease in this group (11.6% vs 3.7%, $P=0.053$). Data on antibiotic administration prior to admission to the ICU was available for 128 out of 168 patients. In both groups of patients, frequent prescription of antibacterial drugs was noted (94.5% and 90%).

We found significant intergroup differences in the results of routine laboratory tests such as lymphocyte count ($P=0003$), neutrophil-lymphocyte ratio ($P=0.004$), C-reactive protein ($P=0.01$), aspartate aminotransferase ($P=0.022$), and vitamin D levels ($P=0.035$) (Table 2). Significant differences were revealed between procalcitonin levels on day 5 ($P=0.031$) and day 10 ($P=0.001$).

Nosocomial infections were first detected on the average on day 6 [3–9] after ICU admission. In total, 232 episodes of nosocomial infections were recorded in 82 patients during their stay in the ICU (35 patient had 2 episodes, 12 patients had 3 episodes, 9 subjects had 4 episodes, 9 patients had 5 episodes, and 1 patient had 6 episodes). Sixty-seven cases of positive cultures were excluded from the analysis (12 blood cultures, 33 lower airway sputum cultures), as these were considered contamination. The most frequent complications included ventilator-associated pneumonia (VAP) (98 [48%] episodes) and bloodstream infection (91 [39%] episodes) (Table 3).

Leading causative agents of bloodstream infection included *A. baumannii* (34%) and *K. pneumoniae* (25%). Gram-positive bacteria were detected less frequently (*Coagulase-negative staphylococci* 15%, *E. faecium* 8%, *E. faecalis* 3%), *Candida albicans* was found in 1% of episodes. Gram-negative bacteria were also among the most frequent causes of infections of the respiratory tract, such as VAP and nosocomial pneumonia/tracheobronchitis (*A. baumannii* — 51%, *K. pneumoniae* — 27%, *Pseudomonas aeruginosa* — 12%). *Aspergillus* spp. was found in a single case of VAP. Urinary tract infections were predominantly caused by *E. faecium* (25%) and *E. faecalis* (25%) (Table 3).

All *Acinetobacter baumannii, Klebsiella pneumoniae*, and *Stenotrophomonas maltophilia* strains were multidrug-resistant.

Compared to COVID-19 patients without nosocomial infection, those with a diagnosed superinfection had an overall longer stay in the ICU (13 [9–18] vs 4 [2–8]; $P<0.001$), longer hospital stay (19 [14–29] vs 15 [11–20]; $P=0.001$) and higher mortality (47 (57.3%) vs 25 (29%); $P<0.001$). Septic shock developed in 52 (63%) patients with infection and was the leading cause of death in these patients.

Table 1. Baseline characteristics and clinical outcomes in COVID-19 patients with/without nosocomial infection.

Parameters	Value in groups		*P* value
	Patients with nosocomial infection, *n*=82	Patients without nosocomial infection, *n*=86	
Clinical parameters			
Age, years	64 [57–76]	67 [57–74]	0.763
Male, *n* (%)	46 (56.1%)	35 (39.3%)	0.066
SOFA, score	2 [1; 3]	2 [1; 2]	0.160
SOFA, score (day 5)	5 [3; 7]	3 [2; 4]	0.060
SOFA, score (day 10)	6 [4; 9]	4 [3; 7]	0.136
SpO_2, %	85 [80; 88]	88 [80; 93]	**0.005**
APACHE II	14 [11; 18]	13 [10; 13]	0.179
Comorbidities			
Coronary heart disease, *n* (%)	37 (45)	42 (48,8)	0.569
Hypertension, *n* (%)	59 (72)	60 (70)	0.846
Use of ACE inhibitors, *n* (%)	32 (39.5)	36 (40.9)	0.853
Chronic kidney disease, *n* (%)	3 (3.7)	10 (11.6)	0.053
Liver disease, *n* (%)	3 (3,75)	3 (3,5)	0.953
Diabetes mellitus, *n* (%)	30 (36.6)	26 (30.2)	0.383
Lung disease, *n* (%)	11 (13.4)	6 (7)	0.167
Cerebrovascular disease, *n* (%)	12 (15.0)	20 (23.5)	0.224
Cancer, *n* (%)	5 (6.1)	11 (12.8)	0.140
Organ support and therapy			
Mechanical ventilation, *n* (%)	75 (67.6)	36 (32.4)	**<0.001**
Mechanical ventilation, days	11 [8; 16]	2 [0; 9]	**<0.001**
Prone position	70 (85.9)	45 (52)	**<0.001**
High-flow oxygen therapy, *n* (%)	40 (50)	27 (31)	**0.033**
High-flow oxygen therapy, days	1 [1; 3]	4 [1; 6]	**0.020**
Renal replacement therapy, *n* (%)	30 (36.8)	8 (9.3)	**0.001**
Norepinephrine, *n* (%)	63 (76.8)	27 (31.3)	**<0.001**
Glucocorticosteroids, *n* (%)	25 (30)	19 (22)	0.139
Antibiotic therapy before ICU (*n*=128)	74/70 (94.5)	54/49 (90.7)	0.450
Outcomes			
LOS in ICU, days	13 [9; 18]	4 [2; 8]	**<0.001**
Hospital stay, days	19 [14; 29]	15 [11; 20]	**0.001**
Mortality in ICU, *n* (%)	47 (57.3)	25 (29)	**<0.001**

Note. Data are presented as the median and percentiles [0.25; 0.75], absolute (*n*) and relative (%) values. ACE, angiotensin-converting enzyme; ICU, intensive care unit; LOS, length of stay; SOFA, sequential organ failure assessment. The Mann–Whitney test and chi-square test were used.

Table 2. Laboratory data of COVID-19 patients with/without nosocomial infection

Parameters	Value in groups		*P* value
	Patients with nosocomial infection, *n*=82	Patients without nosocomial infection, *n*=86	
White blood cell count, 10^9/l	8.0 [6.4; 10.9]	8.0 [6.8; 11.8]	0.53
Lymphocytes, 10^9/l	0,69 [0.5; 0.9]	0,88 [0.6; 1.3]	**0.003**
NLR	10.4 [7.2 ; 14.8]	7.6 [4.3; 13.1]	**0.004**
Platelets, 10^9/l	203 [170; 272]	214 [155; 300]	0.856
Ferritin, μg/l	911 [540; 1700]	628 [402; 1159]	0.070
Interleukin 6, pg/ml	183 [66; 321]	139 [50; 636]	0.901
D-dimer, ng/ml	0.9 [0.56; 2.06]	0.8 [0.4; 1.8]	0.318
Fibrinogen, g/l	4.0 [3.2; 4.9]	4.2 [3.3; 5.0]	0.588
Procalcitonin, ng/ml	0.4 [0.18; 0.97]	0.26 [0.13; 0.65]	0.157
Procalcitonin, ng/ml, day 5	1.52 [0.70; 5.59]	0.41 [0.30; 1.83]	**0.031**
Procalcitonin, ng/ml, day 10	1.32 [0.42; 8.99]	0.54 [0.50; 2.2]	**0.001**
CRP, mg/l	152 [98.9; 237.2]	102.3 [46.9; 159.3]	**0.010**
Vitamin D, ng/ml	9.0 [5.3; 11.9]	12.7 [9.1; 19.7]	**0.035**
AST, U/l	48 [33; 64]	39 [28; 52]	**0.022**
ALT, U/l	35 [26; 54]	30 [22; 47]	0.069
Creatinine, μmol/l	71 [63; 91]	76 [61; 106]	0.376
Bilirubin, μmol/l	12 [8; 16]	11 [8; 15]	0.702
Glucose, mmol/l	8 [7; 11]	8 [6; 11]	0.222

Note. Data are presented as the median and percentiles [0.25;0.75]. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio. The Mann–Whitney test was used.

Discussion

We analyzed all the documented episodes of nosocomial infections in severe and critical COVID-19 patients. To the best of our knowledge, this is one of the first studies in the Russia where the incidence and etiology of superinfection in COVID-19 patients admitted to the ICU is explored in the context of the patient's clinical presentation, results of routine laboratory tests, and outcome.

The incidence of nosocomial infections in the study participants was 48.8%, which is slightly higher than reported elsewhere [5, 7, 11, 12]. This may be due to the differences in the cohort selection, as only severe and critical COVID-19 patients were included.

Nosocomial infections included VAP, tracheobronchitis/nosocomial pneumonia, bloodstream infection, and urinary infections, all of which are typical for ICU-admitted patients. The proportion of patients with bloodstream infections was unusually high (39%) of all the infection episodes. This may have been caused by the ICU staff overload during the peak of the COVID-19 pandemic, as the ICU capacity was increased by 250% to accommodate all the patients requiring intensive care. Special attention was given at that time to counteracting the infections transmitted via respiratory droplets, whereas other methods of infection control (central venous catheter /tracheostoma care) were not sufficiently addressed [13].

The most frequent causative agents of nosocomial infections among patients were multidrug-resistant *A. baumannii* and *K. pneumoniae*. Gram-negative bacteria have been previously reported as the most frequent causes of late nosocomial infections in COVID-19 patients in other countries [14, 15], whereas early superinfection was largely represented by gram-positive microorganisms [16]. *Acinetobacter* spp. and *Klebsiella* spp. are known to be widely spread in Russian Federation [17], and inappropriate use of antibacterial drugs, albeit in line with the guidelines, may have contributed to the development of their multiple resistance [8, 18]. In line with the first version of Russian guidelines on diagnosis and treatment of COVID-19 [8], more than 90% of the patients in our study received empirical antibacterial therapy with the generation III cephalosporins and macrolides. However, the co-infection was quite rare among COVID-19 patients in the ICU, which is consistent with other studies [5, 6]. Also, severe COVID-19 may mimic bacterial sepsis [19], which undoubtedly prompted many doctors to administer antibiotics and was later deemed inappropriate.

Unlike Bartolleti et al [20], we did not observe a significant rate of infections caused by *Aspergillus* spp. This discrepancy may have been caused by the lack of systematic screening for this infection in our clinic.

Progression of the nosocomial superinfection associated with COVID-19 severity. Specifically, we noted significant differences in the SOFA score, SpO_2, lymphocyte counts, neutrophil-lymphocyte ratio, aspartate aminotransferase and C-reactive protein levels between the patients with or without superinfection. All of these parameters were previously associated with disease severity and recog-

nized as negative prognostic factors of COVID-19 outcome [7, 12]. Significant differences between groups in the level of procalcitonin were detected on days 5 and 10. The increase in procalcitonin levels in COVID-19 patients reflects the organism's response to bacterial infection and is independent of the hyperimmune inflammatory response. In our opinion, serial measurement of procalcitonin level helps identify patients with secondary bacterial infection and should be used routinely in patients with COVID-19 both for initiation of antibiotic therapy and assessment of its effectiveness.

Secondary bacterial infection was more frequent in male COVID-19 patients. The risks of severe COVID-19 and unfavorable outcomes are known to be higher for men [5]. Dananche et al [21] reported male sex as a risk factor for VAP which could be attributed to the differences in immune response in men due to genetic factors and hormonal status [22]. Significant differences in vitamin D levels in patients with and without superinfection were found, which is consistent with the protective role of vitamin D in bacterial infections and sepsis [23]. Accordingly, vitamin D level below 10 ng/ml is known to be an independent predictor of unfavorable outcome in patients with severe COVID-19 [24].

Of all the immune-modulating drugs, glucocorticosteroids were used most frequently in our patients. According to the RECOVERY trial [25], the use of dexamethasone has led to a reduction of mortality rate (on day 28) among COVID-19 patients who required mechanical ventilation or oxygen support. Unfortunately, no data on the rate of infections associated with the use of dexamethasone are available. Our groups of patients with/without nosocomial superinfections were balanced in terms of the steroid use. According to Bardi et al [26], steroids were the only medications associated with the risk of nosocomial infections (which was below the level of statistical significance in a multifactorial analysis), yet it did not influence the mortality rate.

In our study, nosocomial infection was associated with higher mortality, longer ICU and hospital stay, and longer duration of mechanical ventilation. In the group of patients with infection, 63% developed septic shock. Complications of infections in ICU-admitted patients are well-known and their effects on the patient outcomes have been described [27, 28]. In a recent study [26], nosocomial infection in COVID-19 patients was reported as an independent negative outcome predictor and was one of the causes of death in 1/3 of patients. Another recent study [29] showed that the development of septic shock in patients with COVID-19 increases the chances of death by 58 times (OR (95% CI): 58.1 (5.97–7812.8), $P<0.001$).

Table 3. Microbiological data by type of infection, *n* (%).

Bacterial/fungal superinfection	*n*=232
Bloodstream infection	***n*=91 (39.2%)**
Acinetobacter baumannii	31 (34.0%)
Klebsiella pneumoniae	23 (25.0%)
Coagulase-negative staphylococci (methicillin-resistant)	14 (15.0%)
Stenotrophomonas maltophilia	8 (9.0%)
Enterococcus faecium	8 (9.0%)
Pseudomonas aeruginosa	3 (3.0%)
Enterococcus faecalis	3 (3.0%)
Staphylococcus aureus	1 (1.0%)
Candida albicans	1 (1.0%)
Ventilator-associated pneumonia	*n*=98 (42.2%)
Acinetobacter baumannii	52 (53.0%)
Klebsiella pneumoniae	25 (26.0%)
Pseudomonas aeruginosa	10 (10.0%)
Stenotrophomonas maltophilia	4 (4.0%)
Staphylococcus aureus (methicillin-resistant)	4 (4.0%)
Proteus mirabilis	2 (2.0%)
Aspergillus fumigatus	1 (1.0%)
Nosocomial pneumonia / tracheobronchitis	*n*=31 (13.4%)
Acinetobacter baumannii	14 (45.0%)
Klebsiella pneumoniae	10 (32.0%)
Pseudomonas aeruginosa	5 (16.0%)
Stenotrophomonas maltophilia	2 (6.0%)
Staphylococcus aureus (methicillin-resistant)	1 (3.0%)
Urinary infection	*n*=12 (5.2%)
Enterococcus faecium	3 (25.0%)
Enterococcus faecalis	3 (25.0%)
Klebsiella pneumoniae	2 (16.7%)
Acinetobacter baumannii	2 (16.7%)
Pseudomonas aeruginosa	1 (8.2%)
Candida non-albicans (*C.glabrata. C.tropicalis*)	2 (16.7%)
Candida albicans	2 (16.7%)

Our study has several limitations. Only infections documented by culture were included and, therefore, some episodes could be missing. This study was limited to a single center, with its local pattern of antimicrobial resistance, which may limit the generalizability of the findings. The retrospective design reduces control over multiple confounders and data collection.

Conclusion

In patients with severe and critical COVID-19, a high incidence of nosocomial infections was observed. Nosocomial infection was associated with the initial severity of the disease at presentation as well as with the unfavorable outcome. Most frequently, antibiotic-resistant strains of gram-negative bacteria were the causative infectious agents. Procalcitonin is a useful biomarker for identifying bacterial infection in patients with COVID-19.

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Assessment of Clinical Efficacy of Dexamethasone in Patients with Moderate COVID-19

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Анализ клинической эффективности дексаметазона у пациентов со среднетяжелым течением COVID-19

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Summary

The host immune response, primarily manifested by hypercytokinemia, obviously plays a key role in the development of severe novel coronavirus disease, COVID-19. Currently, numerous therapies aimed at suppressing the hyperinflammatory response and the «cytokine storm» are being investigated. One of these methods is the use of corticosteroids, particularly dexamethasone.

The aim was to assess the clinical efficacy of dexamethasone in patients with moderate bilateral multifocal pneumonia caused by SARS-CoV-2 virus.

Material and methods. Sixty-nine patients aged from 31 to 88 years hospitalized in Almazov National Research Center and the Semashko City Hospital No 38 with SARS-CoV-2 coronavirus infection complicated by moderate (semiquantitative visual pulmonary lesion grading system CT 2–3 corresponding to 25–50% and 50–75% parenchymal involvement, respectively) community-acquired bilateral multifocal pneumonia were retrospectively studied. Group 1 included 39 patients with moderate coronavirus infection who received therapy according to the current version of the temporary guidelines (TG) of the Ministry of Health of the Russian Federation, including dexamethasone. The drug was administered parenterally twice daily in a dosage of 12 mg in the morning and 8 mg in the evening for the first three days, then the dose was gradually reduced over 5–7 days. No Interleukin-6 inhibitors were administered to patients in this group. Group 2 was composed of 30 patients who received therapy according to the current version of TG, including a parenteral interleukin-6 inhibitor (tocilizumab, olokizumab, or sarilumab) following the standard regimen. Patients in this group were not administered with dexamethasone.

Results. CT scans corresponding to severity grade 3 and 4 (50–75% and >75% involvement, respectively) lung lesions on Day 7 were found in 35.89% of group 1 patients, while similar CT scans were found in 50% of patients who received interleukin-6 inhibitors (P=0.33). On Day 14 no significant differences in this parameter were revealed as well. Duration of fever in the dexamethasone group was 3.69 (0.62; 6.76) days, while in the control group it was 3.95 (0.61; 7.29) days (P=0.98). There was a tendency to decreased blood C-reactive protein (CRP) values in the dexamethasone group on days 5 and 7. The frequency of transfer of patients to the ICU and hospital stay duration did not differ significantly between the groups.

Conclusion. Dexamethasone has comparable clinical efficacy with IL-6 antagonists in the comprehensive treatment of patients with moderate COVID-19 disease, which is confirmed by the chest CT evolution, duration of fever, and changes in serum CRP.

Keywords: COVID-19; glucocorticoids; interleukin-6 inhibitors

Conflict of interest. The authors declare no conflict of interest

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Introduction

In 2019, the SARS-CoV2 virus, which causes the novel coronavirus infection, was detected for the first time in Wuhan, Hubei province, China [1]. In a short period of time, the outbreak of this disease reached pandemic proportions. According to statistics, as of March 12, 2021, 119,748,246 cases had been identified worldwide. Russia ranks fourth among all countries in the number of cases (4,341,381) [2, 3].

Coronavirus infection remains a major challenge for scientists and clinicians worldwide. The clinical picture of COVID-19 has a wide range of manifestations, from asymptomatic and mildly symptomatic disease to severe pneumonia with extensive lung involvement and hyperinflammatory syndrome [4, 5].

Some authors identify three degrees of severity of coronavirus infection: mild (with nonspecific symptoms such as malaise, dry cough, fever), moderate (viral pneumonia with cough, fever and, possibly, hypoxia), and severe (extrapulmonary systemic hyperinflammatory syndrome). Obviously, the main role in severe COVID-19 is played by the host immune response, which primarily manifests as hypercytokinemia [6, 7].

Numerous treatment approaches aimed at suppressing the hyperinflammatory response are being studied, but none of them has convincing evidence of efficacy. The use of corticosteroids, particularly dexamethasone, is one of these treatment modalities. Currently, many studies evaluating the efficacy and safety of dexamethasone for patients with moderate to severe coronavirus infection have been conducted [8, 9].

In March 2020, Jamaati H. et al. studied 50 patients, 25 of whom received dexamethasone 20 mg for the first five days of hospitalization and then 10 mg during days six through ten. According to the results of this study, 92% of patients in the dexamethasone group and 96% in the control group (P=0.500) required noninvasive ventilation, while 44% in the dexamethasone group and 52% in the control needed mechanical lung ventilation. The study authors pointed out that improvement on CT scans was seen in 40% of patients in the dexamethasone group vs 12% of patients in the control group [10].

A controlled, open-label, randomized trial RECOVERY found a reduction in 28-day mortality among patients who required oxygen therapy or ventilator support and were prescribed dexamethasone for ten days. There was also a reduction in 28-day mortality when dexamethasone was used seven days after the onset of disease. Among patients who received oxygen therapy, dexamethasone use was associated with a lower risk of being switched to invasive ventilation, and in those who were already on invasive ventilation it was related to a higher chance of successful weaning from mechanical ventilation [12].

However, according to a meta-analysis (March 2020), the use of corticosteroids can reduce viral clearance and increase length of stay [7]. In December 2020, the results of another meta-analysis [9] were published, which included randomized clinical trials and observational cohort studies evaluating the effect of corticosteroids in COVID-19. The authors reported that the effect of dexamethasone on viral clearance and the development of secondary infections could not be reliably assessed due to insufficient data. In contrast, they confirmed a significant reduction in 28-day mortality when using corticosteroids, particularly dexamethasone, in COVID-19. Several medical societies have decided to include dexamethasone in the treatment protocol for patients with COVID-19 [11].

In summary, corticosteroids, on the one hand, can indeed suppress the hyperimmune response and, on the other hand, increase the risk of opportunistic or nosocomial infections, inhibit the hypothalamic-pituitary-adrenal axis, induce hyperglycaemia in predisposed persons or in patients with diabetes mellitus, and reduce viral clearance [8, 13].

Due to contradictory data on usefulness of steroids in COVID-19, we conducted a retrospective study to evaluate the effectiveness of dexamethasone in patients with moderate bilateral multifocal viral pneumonia caused by SARS-CoV-2.

Aim — to determine the clinical efficacy of dexamethasone in patients with moderate bilateral multifocal viral pneumonia caused by SARS-CoV-2 virus.

Material and Methods

A cohort retrospective clinical study was performed in 69 patients aged 31 to 88 years (mean age 60 years) with coronavirus infection caused by SARS-CoV-2, complicated by moderate community-acquired bilateral multifocal viral pneumonia and admitted to Almazov Scientific Research Center and the Semashko City Hospital No.38, Saint Petersburg. All patients were admitted to the intensive care wards of infectious diseases departments and required low-flow oxygen therapy through nasal catheters or a mask due to clinical manifestations of respiratory failure.

Inclusion criteria were patient's age 18 to 90 years, moderate clinical manifestations of COVID-19 (fever above 38.0 °C, respiratory rate >22 /min, dyspnea on exercise, SpO_2 <95%, serum C-reactive protein (CRP) level >10 mg/l, abnormal chest CT or X-ray characteristic of viral damage (moderate

severity, corresponding to CT grade 2–3 according to the semi-quantitative visual assessment scale).

Exclusion criteria were autoimmune disease, cancer, routine glucocorticoid therapy, history of chemotherapy, and chronic kidney disease (CKD).

Group 1 included 39 patients with moderate coronavirus infection who received therapy according to the Temporary Guidelines (TG) on prevention, diagnosis and treatment of novel coronavirus infection (COVID-19) of the Ministry of Health of the Russian Federation, Version 8.1 (01.10.2020), including dexamethasone. Dexamethasone was administered on the following indications: combination of CT findings (progression of lesion volume over 3–5 days with two or more of the following: decreased SpO_2 <93% on ambient air, CRP level >40 mg/l; fever >38°C for 5 days). Dexamethasone treatment was started, on average, on day 10 from the onset of the disease. The drug was administered parenterally twice daily in a dosage of 12 mg in the morning and 8 mg in the evening during the first three days, then the dose was tapered over 5–7 days. Interleukin-6 inhibitors were not used in patients of this group.

Group 2 was composed of 30 patients who received therapy according to the current version of TG of the Russian Ministry of Health, including parenteral interleukin-6 inhibitors (tolicizumab, olokizumab, sarilumab) in standard regimens. Indications for prescription of interleukin-6 inhibitors according to TG were progression of interstitial lung damage on chest CT scan in combination with two and more of the following: progressive decrease in SpO_2; CRP>60 mg/l or an increase in CRP 3 or more times its value on admission; fever >38°C for 5 days; WBC count $<3.0\times10^9$/l; absolute lymphocyte count $<1\times10^9$/l; blood ferritin level >500 ng/ml; plasma IL-6 level >40 pg/ml. Patients of this group did not receive dexamethasone or other glucocorticoids.

The following criteria were used to evaluate the efficacy of treatment: chest CT scan on days 1, 7, and 14 from admission, presence/absence of body temperature elevation (>37.2°C), C-reactive protein, ferritin, WBC and lymphocyte counts on days 1, 2, 3, 5, 7, and 10.

Comparative analysis of quantitative variables was performed using Mann–Whitney test; qualitative variables were analyzed using Fisher's exact test. For quantitative variables the results were presented as *Me* (*Q1; Q3*) (median and interquartile range). For all statistical calculations, the level of significance was set to $P<0.05$.

Results

There were no significant differences between the groups in terms of gender, age, respiratory rate, use of noninvasive respiratory therapies, and comorbidities at baseline (Table 1).

According to data presented in Table 2, on day 7 CT findings corresponding to 3–4 degree of lung involvement were revealed in 35.89% of patients from group 1, while similar CT patterns were found in 50% of patients receiving interleukin-6 inhibitors ($P=0.33$). On day 14 there were also no significant differences in this parameter. Duration of body temperature elevation in dexamethasone group was 3.69 (0.62;6.76) days, and 3.95 (0.61;7.29) days in the control group ($P=0.98$). There were no statistically significant differences between the groups in changes in peripheral blood lymphocyte count and serum C-reactive protein level during the first 10 days after enrollment. The trend toward lower CRP values on days 5 and 7 in the dexamethasone group is worth noting. The rate of transfers to ICU and length of hospital stay also did not differ significantly.

Discussion

Glucocorticoids have previously been used for coronavirus-associated syndromes, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). However, the evidence base for their efficacy in these infections was rather limited (level of evidence 3) due to the lack of randomized controlled trials [13–15, 17].

The RECOVERY study was designed to perform a rapid and reliable assessment of the effect

Table 1. Comparative characteristics of groups by sex, age and comorbidities.

Parameters	Values in groups		*P*
	Group 1, *n*=39	Group 2, *n*=30	
Age	60.02 (56.24; 63.8)	61.20 (55.54; 72.53)	0.87
Sex	24 female/15 male	17 female/13 male	0.81
Respiratory rate more than 22 per minute on admission	39	30	1.00
Oxygen therapy through a face mask with a flow rate up to 15 l/min	39	29	1.00
Non-invasive mechanical lung ventilation	0	1	1.00
Comorbidities			
Diabetes mellitus	9 (23.07%)	3 (10%)	0.21
Obesity	7 (17.94%)	6 (20%)	1.000
Hypertension	25 (64.01%)	13 (43.33%)	0.095
Coronary heart disease	11 (28.21%)	4 (13.33%)	0.16
History of cancer	0	1 (3.33%)	0.44

Table 2. Comparative characteristics of groups by main parameters of clinical outcome and laboratory markers.

Parameter	Values in groups		*P*
	Group 1, *n*=39	Group 2, *n*=30	
CT grade 3–4, day 7	14 (35.89%)	15 (50%)	0.33
CT grade 3–4, day 14	4 (10.25%)	3 (10%)	1.00
Fever duration, days	3,69 (0,62; 6,76)	3,95 (0,61; 7,29)	0.98
C-reactive protein, mg/l			
Day 1	29.26 (22.3; 36.25)	59.32 (32.99; 85.65)	0.14
Day 3	28.02 (10.76; 45.28)	49.96 (39.35; 66.12)	0.15
Day 5	28.32 (15.04; 41.61)	57.38 (40.43; 74.33)	0.14
Day 7	17.41 (11.67; 23.15)	24.36 (20.59; 28.13)	0.1
Day 10	22.98 (4.1; 41.86)	18.22 (9.49; 26.95)	0.17
Blood lymphocytes, absolute count per mm^3			
Day 1	1542 (1360; 1724)	1180 (994; 1366)	0.02
Day 5	1080 (760; 1400)	1350 (1135; 1565)	0,09
Day 7	1757 (1450; 2064)	1460 (742; 2178)	0,15
Day 10	1897 (1290; 2504)	1280 (777; 1783)	0,07
Transfer to ICU, patients	0	1	1.00
Adverse clinical outcome, patients	0	1	1.00
Length of hospital stay, days	15.17 (12.82; 17.52)	12.0 (8.18;15.82)	0.08

of available COVID-19 treatments on the 28-day mortality rate. This parameter is an essential though not the only indicator of treatment efficacy. In a randomized clinical trial involving 299 adults with moderate to severe COVID-19-induced ARDS, dexamethasone significantly (RR, 0.84; 95% CI, 0.54–1.32) increased the number of ventilator-free days in the ICU during the first 28 days of illness [12].

However, some researchers have raised concerns that high doses of corticosteroids (equivalent to 30 mg of dexamethasone per day) for viral pneumonia may be associated with adverse outcomes [18].

An open randomized multicenter trial conducted in Spain involving 277 patients with ARDS unrelated to COVID-19 showed a 15% reduction in 60-day mortality (from 36% to 21%) in patients treated with dexamethasone [20].

A recent meta-analysis including data from seven studies of glucocorticoid use in COVID-19 patients in critical care, including RECOVERY, showed that among patients receiving oxygen, dexamethasone use was associated with a lower risk of invasive ventilation or, for those already on invasive ventilation support, with a higher chance of successful weaning. Moreover, dexamethasone use increased the likelihood of a favorable outcome (RR 0.64; 95% CI, 0.50–0.82; $P<0.001$) and discharge from hospital within 28 days [19].

Nevertheless, it is important to note the heterogeneity of the groups compared in different RCTs and meta-analyses, all in terms of disease severity, doses and regimens of glucocorticoid administration. Slower clearance of viral RNA was observed in patients with SARS, MERS and influenza treated with systemic glucocorticoids, but the clinical significance of this fact is unknown [21]. In contrast to SARS, in which viral replication peaks in the second week of illness [22], viral shedding in SARS-CoV-2 appears to be significantly higher in the early stages and declines sharply on week 2–3 [23].

Our data demonstrated clinical efficacy of dexamethasone comparable to IL-6 antagonists in a group of patients with moderate COVID-19. The effect of dexamethasone on the 28-day mortality in patients with COVID-19 on respiratory support suggests that immunopathological processes may predominate as early as during the second week of disease, with active viral replication playing a secondary role. This hypothesis cautions against extrapolating the clinical effect of dexamethasone in patients with COVID-19 to those with other viral respiratory diseases [16, 24, 25].

Certain limitations and drawbacks of the study should be noted. The patient assessment using severity scales, such as SOFA, SAPS or APACHE-II, was not used, since only patients with moderate COVID-19 were included in the retrospective analysis. Obviously, a patient with respiratory failure is affected by a variety of disease-modifying factors such as antiviral and antibacterial therapies, anticoagulant regimens, sedation and analgesia, respiratory support techniques, infectious complications, and others. Since it is often extremely difficult to discern the influence of a particular factor in real practice, we have assumed an equal impact of these factors on the patients in the studied groups. Also, it is necessary to bear in mind that only a single-factor analysis was performed. Thus, further research in this area through conducting a prospective randomized controlled trial is necessary to confirm the results obtained.

Conclusion

Dexamethasone has comparable clinical efficacy to IL-6 antagonists in the comprehensive treatment of patients with moderate COVID-19, as confirmed by the changes in chest CT scan, duration of elevated body temperature, as well as the trends in serum CRP level.

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Diaphragm Function Parameters in Patients with Severe COVID-19

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Показатели функции диафрагмы у пациентов с COVID-19 тяжелого течения

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Summary

The aim of the study was to investigate the feasibility of predicting the need for mechanical ventilation in patients with severe COVID-19 disease using ultrasound assessment of diaphragm function.

Material and methods. An open prospective pilot study included 60 patients diagnosed with the novel coronavirus infection, who, at the time of admission to the intensive care unit (NEWS score > 6), underwent ultrasound assessment of diaphragm excursion, thickness and the diaphragm thickening fraction. Group 1 (n=30) included patients who did not require mechanical ventilation, and group 2 (n=30) consisted of patients who were subsequently transferred to mechanical ventilation.

Results. Patients in group 2 had significantly lower diaphragm function parameters (left excursion value (P<0.001), right excursion value (P<0.001), diaphragm thickness on inspiration (P=0.043), and thickening fraction (P<0.001) than patients in group 1.

Conclusion. Decreased diaphragm excursion of less than 17.1 mm on the right side is a predictor of initiation of mechanical ventilation in patients with the COVID-19 infection (sensitivity 93.3%, specificity 76.7%). Morphological examination in deceased patients of group 2 revealed pericellular and perivascular edema, venular thrombosis, endoneurial edema, and sludge in the lumen of arterioles.

Keywords: novel coronavirus infection; COVID-19; complications; diaphragm

Conflict of interest. The authors declare no conflict of interest.

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Introduction

ACE2 receptors of alveolar cells of type II are the «entrance gate» of the novel coronavirus infection (COVID-19) into the lungs, which causes lung damage of varying severity and prevalence in all patients who died of COVID-19 [1, 2]. Symptoms of viral infection in moderate, severe and critical disease include reduced oxygen saturation, dyspnea, low oxygenation index, i.e., represent hypoxia [3]. The volume of pulmonary involvement according to CT scan does not always correlate with the severity of respiratory failure, which warrants the search for additional drivers of respiratory failure in patients with COVID-19 [4–6]. One of these factors could be the functional status of the diaphragm,

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which is suggested by the presence of ACE2 receptors in the human diaphragm and SARS-CoV-2 viral infiltration of the diaphragm in patients with severe COVID-19 [7–9].

The diaphragm is known to be the main inspiratory respiratory muscle and plays a leading role in spontaneous ventilation. Unilateral phrenic nerve blockade leads to a decrease in pulmonary ventilation down to 30% of the baseline [10–12]. In COVID-19, impaired function and/or structure of the diaphragm may be due to a comorbidity (diabetic polyneuropathy), individual characteristics, direct neurotoxic effect of the virus, of respiratory neuropathy of critical illness [13–15].

The aim of the study was to evaluate the feasibility of predicting mechanical ventilation in patients with severe novel coronavirus infection using ultrasound assessment of diaphragmatic function.

Material and Methods

This open, prospective pilot study included 60 patients diagnosed with the novel coronavirus infection at the moment of their admission to the intensive care unit, who had progressive respiratory failure by days 6–7 from the onset of the disease.

All patients had clinical manifestations of viral pneumonia, confirmed by a positive RT-PCR test for SARS-CoV-2 RNA on admission and a characteristic radiological presentation on chest CT (CT grade 2–4 according to the semi-quantitative visual assessment scale).

The patients were assigned to two groups: group 1 (n=30) included patients who did not require invasive ventilation, and group 2 (n=30) comprised patients who were put on mechanical ventilation within the first 6-12 hours of admission to the ICU.

The patients placed on the ventilator not due to the progression of coronavirus infection, but for other reasons identified during differential diagnosis (acute cerebrovascular event, pulmonary embolism, etc.) were excluded from the study.

Severity assessment at the moment of admission to ICU was performed using the National Early Warning Score (NEWS) [16]. General characteristics of patients are shown in Table 1.

As seen from Table 1, patients in both groups did not differ significantly in age, sex, body mass index, volume of lung tissue involvement on CT scan, as well as in severity of disease and comorbidities.

The diaphragm was examined using a General Electric Ligiq e R8 ultrasound scanner (General Electric, USA). The function of the diaphragm was assessed by determining its right and left excursion and thickening during breathing [17, 18].

Assessment of right and left diaphragm excursion was performed in supine position using low-frequency probes (convex or phased array transducers). The probe was placed between the midclavicular and anterior axillary lines with the scanning beam oriented medially in the dorsocranial direction, i. e., the ultrasound beam crossed the diaphragm at right angles. In M-mode, the amplitude of motion of posterior third of diaphragm during normal breathing was measured.

Assessment of diaphragm thickening was performed in the supine position using a high-frequency linear transducer. The study was performed in B-mode. The transducer was placed in the coronary plane along the midaxillary line at the level of the costophrenic sinus. The diaphragm was visualized at its interface with the chest wall with assessment of its maximal thickness on inhalation and minimal thickness on exhalation.

Based on the diaphragm thickness measurement, the thickening fraction was calculated as the ratio of diaphragm thickness on inspiration to diaphragm thickness on expiration.

In the clinical case below, a specimen of the diaphragm of a patient who died of COVID-19 is demonstrated. The sample was taken from the lumbar portion corresponding to the area of ultrasound examination. For microscopic examination of preparations stained with hematoxylin and

Table 1. General characteristics of patients.

Parameters	Value in groups		*P*
	Group 1	Group 2	
Number of patients, *n*	30	30	
Age, ($M\pm\sigma$)	74.4±17.28	70.23±18.12	0.482
Males, *n* (%)	18 (60)	14 (47)	0.438
Females, *n* (%)	12 (40)	16 (53)	0.565
Body mass index, kg/m^2 ($M\pm\sigma$)	28.22±3.16	28.21±3.15	0.894
Severity on the NEWS scale on admission to ICU, points, ($M\pm\sigma$)	6.4±1.9	6.0±2.0	0.585
Oxygen therapy, *n* (%)	8 (26,7)	6 (20)	
High flow rate oxygenation, *n* (%)	12 (40)	12 (40)	
Noninvasive lung ventilation, *n* (%)	10 (33,3)	12 (40)	
Volume of lung involvement ($M\pm\sigma$), %	42.7±27.0	55.23±27.15	0.096
Comorbidities			
Diabetes mellitus, *n*	30	27	
Hypertension, *n*	26	24	

Table 2. Parameters of diaphragmatic function in patients with the novel coronavirus infection (*M±σ, Me* [0,25; 0,75]).

Parameters	Values in groups		*P-value*
	1	2	
Left hemidiaphragm excursion, cm	1.92±0.39	1.29±0.21	<0.001
Right hemidiaphragm excursion, cm	2.21±0.68	1.46±0.2	<0.001
P-value	0.02	0,039	
Diaphragm thickness on expiration, cm	0.21±0.07	0.26±0.18	0,3
Diaphragm thickness on inspiration, cm	0.37±0.13	0.32±0.19	0.043
P-value	0,004	<0,001	
Thickness fraction	1.72 [1.16; 2.32]	0.93 [0.81; 1.02]	<0.001

eosin, a medical transmitted light microscope mVizo-101 (LOMO, Russia) was used. Examination and microphotography were performed using Planamat 5/0.10 objective with XT0028 video attachment, the linear magnification of the microscope was 63–240.

Statistical analysis of the results was performed using the IBM SPSS Statistics (Version 25) software package. All data were checked for normality of distribution using Shapiro–Wilk test. To compare qualitative variables in unrelated samples we used Fisher exact test, to compare quantitative parameters with non-normal distribution in unrelated samples we used Mann–Whitney *U*-test, in related samples the Wilcoxon *T*-test was employed. To analyze correlation, we used Spearman's rank correlation *R* coefficient. Logistic regression with regression model was used for probability prediction. Using binary logistic regression (forward LR method), we investigated the dependence of the dichotomous variable (starting the mechanical ventilation) on the independent variables (diaphragm excursion, diaphragm thickening fraction). ROC analysis was used to assess the quality of binary classification, and the Youden index (maximization of the sum of sensitivity and specificity) was applied to select the optimal cut-off point. The null hypothesis of lack of significant differences was rejected at $P \leqslant 0.05$.

Results and discussion

The results of ultrasound examination of the diaphragm in the patients are presented in Table 2. The parameters of diaphragm function (left excursion, right excursion, diaphragm thickness on inhalation, and thickening fraction) differed significantly between patients in groups 1 and 2. No significant differences were observed only for diaphragm thickness on exhalation.

In addition, the right and left hemidiaphragm excursion values differed between the groups. Interestingly, Boussuges A. et al. in their study found no differences in right and left hemidiaphragm excursion in healthy patients [19]. We attribute our findings to such specific features of ultrasound imaging of the left hemidiaphragm as poor acoustic window (gastric bubble on the left side). Based on the scientific literature data, we deem it appropriate to assess the excursion in the area with the best acoustic window, i. e., on the right side [20].

Analysis of the correlation between the left hemidiaphragm excursion and ventilation support requirement revealed a significant (P<0.001) strong correlation with the Spearman *r* value of -0.731. At the same time, higher values of hemidiaphragm excursion were more commonly found in the group of patients who were not placed on respiratory support.

Analysis of relationship between the right hemidiaphragm excursion and mechanical ventilation requirement revealed a significant (P<0.001) moderate correlation (Spearman *r*, -0.576). At the same time, higher hemidiaphragm excursion was more commonly seen in the patients who did not require mechanical ventilation.

Analysis of the correlation between diaphragm thickening fraction and ventilation requirement revealed a significant (P<0.001) strong correlation (Spearman *r*, -0.477). At the same time, higher values of the diaphragm thickening fraction were more commonly seen in patients from group 1.

Despite significant intergroup differences in diaphragm thickness on inspiration, correlation analysis of this variable was not performed due to its secondary character.

To predict the probability of ventilator support initiation based on the parameters of diaphragm function, we developed a logistic regression model. At that, the left hemidiaphragm excursion values lost their statistical significance (P=0.108). Hence,

$$\mathbf{p=1/(1+e^{-z})}$$

where P is the probability of ventilator support initiation, e=2,718… represents the base of natural logarithms; z = a + (B1 × X1) + (B2 × X2); A (regression equation constant) = 27.479 (P=0.001); B1 = –11.365 (P=0.003); X1 is diaphragm thickness fraction; B2 = –7.097 (P=0.006); X2 is right hemidiaphragm excursion; Thus, z = 27,479 – 11,365 × X1 – 7,097 × X2.

If the calculated probability was greater than 0.5, the patient was assigned to group 2 (patients on mechanical ventilation).

The percentage of correct predictions in the studied patient sample was 91.7%; the Nagelkerke

R-squared was 0.848. Therefore, the predictive model can be considered adequate in general. The Hosmer–Lemeshow goodness-of-fit test showed agreement between the model and the real data (*P*=0.510).

Based on the predicted values, an ROC curve was plotted to assess the prognostic significance of the regression model (Fig. 1).

The area under the curve for the predicted values was 0.977 (*P*<0.001). The area values between 0.946 and 1.000 corresponded to the 95% confidence interval. The regression model predicts initiation of mechanical ventilation based on independent variables (diaphragm excursion, diaphragm thickening fraction) with a sensitivity of 93.3% and specificity of 93.3% (cut-off point 0.529).

A ROC-curve was plotted to assess the sensitivity and specificity of right hemidiaphragm excursion and diaphragm thickening fraction as predictors of critical novel coronavirus infection (COVID-19). The area under the curve for the right hemidiaphragm excursion was 0.832 (*P*<0.001). The area values from 0.719 to 0.946 corresponded to the 95% confidence interval.

The area under the curve for the diaphragm thickening fraction was 0.775 (*P*<0.001). The area values from 0.657 to 0.893 corresponded to the 95% confidence interval.

Curves evaluating the prognostic significance of right hemidiaphragm excursion and diaphragm thickening fraction in ROC analysis are shown in Fig. 1. The cutoff values of right hemidiaphragm excursion as a predictor of extremely severe course of novel coronavirus infection (COVID-19) of 17.1 mm or less had a sensitivity of 93.3% and a specificity of 76.7%. The findings were consistent with those of Boussuges A., who showed that diaphragm excursion in healthy individuals was 18±3 mm in men and 16±3 mm in women [19]. Consequently, the decrease of this parameter has a prognostic value for possible switching the patient to ventilator support.

The cutoff values of diaphragm thickening fraction for predicting a critical COVID-19) of 1.3 times or less had a sensitivity of 70% and a specificity of 60%.

The severity of respiratory failure may be related to the direct myo- and neurotoxic effects of the virus [8]. To verify the morphology underlying the diaphragmatic dysfunction, we performed a single morphological study of the diaphragm and phrenic nerve of a patient who died from COVID-19. The specimens showed pericellular and perivascular edema, venular thrombosis, endoneurial edema, and sludge in the arteriolar lumen (Fig. 3).

The morphological changes of the phrenic nerve in this case can explain the acute decompensation of respiratory failure with respiratory arrest in patients with COVID-19.

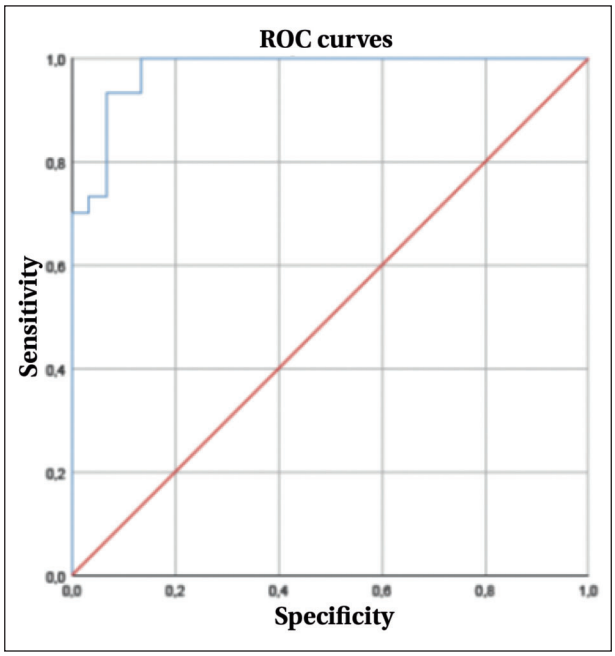

Fig. 1. A curve for assessing the prognostic significance of the regression model.

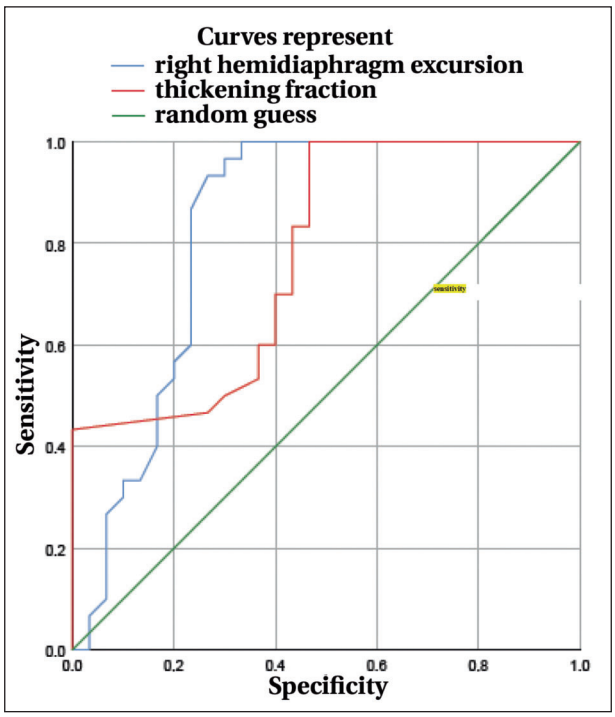

Fig. 2. The curves of prognostic value assessment of the right hemidiaphragm excursion (shown in blue), the diaphragm thickening fraction (in red) in ROC analysis.

The obtained morphological data warrant further investigation of the relationship between diaphragm function and its morphological changes in patients with COVID-19.

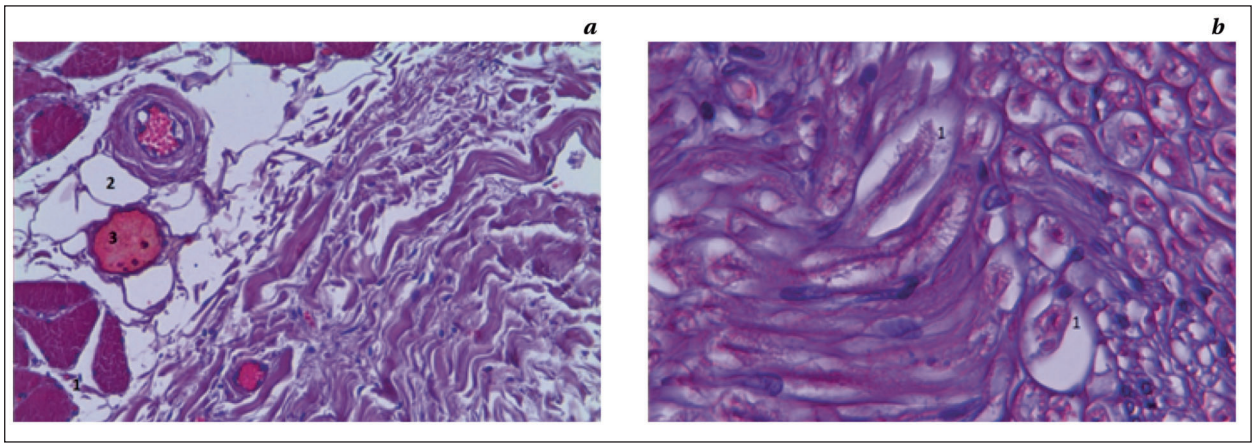

Fig. 3. Specimen of the diaphragm (*a*) and phrenic nerve (*b*) of a patient who died of COVID-19.
Note. Hematoxylin and eosin staining. XT0028 video attachment. *a* — ×20 magnification. Pericellular (1) and perivascular (2) edema, venous thrombosis (3). *b* — ×63 magnification. Endoneural edema (1).

Conclusion

Patients with critical novel coronavirus infection who require mechanical ventilation demonstrate diaphragm dysfunction with its reduced motion and abnormal contraction.

Decreased right hemidiaphragm excursion less than 17.1 mm is a predictor of ventilator support in COVID-19 patient with a sensitivity of 93.3% and a specificity of 76.7%.

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Spontaneous Intramuscular Hematomas in Patients with Severe COVID-19 (Case Report)

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Спонтанные внутримышечные гематомы у пациентов с тяжелым течением COVID-19 (клиническое наблюдение)

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Summary

Aim of the study. To evaluate the risk factors for the occurrence of intramuscular hematomas in patients with severe coronavirus infection receiving anticoagulant therapy.

Materials and methods. Intramuscular hematomas in five patients with severe COVID-19 disease are reported in the paper. The criteria for selecting patients for the study included respiratory distress requiring oxygen, radiographic signs of severe pneumonia, anticoagulant therapy using low molecular weight heparin (LMWH), and spontaneous intramuscular hematoma. Clinical manifestations, blood coagulation results, conservative and surgical management were analyzed.

Results. Standard regimen anticoagulation therapy in patients with coronavirus infection requires vigilance because of a risk of development of hemorrhagic complications.

Conclusion. When assessing a patient with hematomas, an emphasis should be given to examination of patients and changes in hemoglobin and hematocrit levels. Best strategy of anticoagulant therapy for patients with coronavirus infection and high risk of VTE, as well as optimal laboratory monitoring during LMWH administration are yet to be explored.

Keywords: intramuscular hematoma; anticoagulant therapy; coronavirus infection

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Coagulopathy and thrombotic complications are severe complications of coronavirus infection [1]. Disorders of blood coagulation system occurring in SARS-CoV-2 infection result from immune and cellular elements of disease pathogenesis [2]. Vascular manifestations of COVID-19 are associated with thrombus formation both in the microcirculatory system and in large vessels with a variety of clinical manifestations including pulmonary, gastrointestinal, cardiovascular, and neurological ones. Venous and arterial thrombosis, emboli, parenchymal infarcts, erythematous lesions occur in patients [2]. Coagulopathy in COVID-19 associates with a high risk of death. Analysis of autopsy data of patients who died from COVID-19 indicates multiple thromboses of small pulmonary vessels and associated multiple hemorrhages in alveoli, as well as neoangiogenesis, alongside with diffuse alveolar damage [3]. Prolonged bed rest, vascular catheters, severe baseline comorbidities (cardiovascular diseases, obesity, diabetes mellitus), frequent glucocorticoid therapy also con-

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tribute to thrombotic complications. According to the Temporary Guidelines of the Russian Ministry of Health, low molecular weight heparins (LMWH) or unfractionated heparin (UFH), at least in preventive doses, are indicated for all hospitalized patients, unless there are contraindications. LMWH are preferable, UFH is used when they are unavailable or in severe renal failure [3]. Thus, anticoagulation is mandatory in patients with COVID-19. The dosage of heparin could be increased to an intermediate or therapeutic level in patients with high and extremely high D-dimer level or if additional risk factors of venous thromboembolic complications are present, as well as in severe COVID-19 or in patients admitted to ICU. In patients with obesity (body mass index > 30 kg/m^2), a 50% increase in the prophylactic dose should be considered. The use of anticoagulants in severe COVID-19, especially in progressive elevation of D-dimer level significantly improves patient survival rates [1, 4]. For critically ill patients (i.e., those admitted to intensive care unit) with confirmed or highly probable COVID-19, increased doses of LMWH to prevent VTE are also recommended by international clinical protocols [4].

The use of anticoagulants associates with an increased risk of hemorrhagic complications, primarily gastrointestinal (GI) bleeding. Besides, intramuscular hematomas of various localizations related to anticoagulant administration have been described in COVID-19 patients [5, 6, 7–10]. In some cases patients received anticoagulant therapy in combination with antiaggregant agents [11]. When there are no external signs of hematoma, this complication can present with nonspecific signs and symptoms, such as anemia, low back and anterolateral abdominal discomfort and paresthesia, and hypogastric pain, or, exceptionally, hemodynamic instability with hypovolemic (hemorrhagic) shock [5, 8–13].

This paper reports a series of five clinical cases of hemorrhagic complications of coronavirus infection in patients on anticoagulant therapy.

Material and Methods

We retrospectively analyzed intramuscular hema-tomas in five of 66 patients with the novel coronavirus infection treated in the Department of Critical Care and Anesthesiology of the A. L. Polenov Russian Research Neurosurgical Institute, a branch of the V. A. Almazov Scientific Research Center. The work was performed in accordance with the requirements of the Declaration of Helsinki of the World Medical Association (2013). The mean age of the patients was 68±4.7 years, of whom 35 were men and 31 were women. The most frequent comorbidities were hypertension (43 patients), coronary heart disease (35 patients), type 2 diabetes mellitus (15 patients), chronic pyelonephritis (11 patients), and 3–4 degree obesity (8 patients). All patients received therapy, including anticoagulants, according to the temporary guidelines on prevention, diagnosis and treatment of the novel coronavirus infection (COVID-19) (Version 9), as well as in accordance with the local protocol of the V. A. Almazov Scientific Research Center. The patients had no GI hemorrhages, but five of them developed intramuscular hematomas of various localizations. Hematomas occurred in the pectoral muscles (2 cases), anterior abdominal wall muscles (two cases), right psoas muscle (1 case).

The criteria for selection of patients for the study included respiratory failure requiring oxygen therapy, radiological signs of severe pneumonia (CT grade 3–4 according to semi-quantitative visual assessment scale), anticoagulant therapy with LMWH, and spontaneous intramuscular hematoma(s).

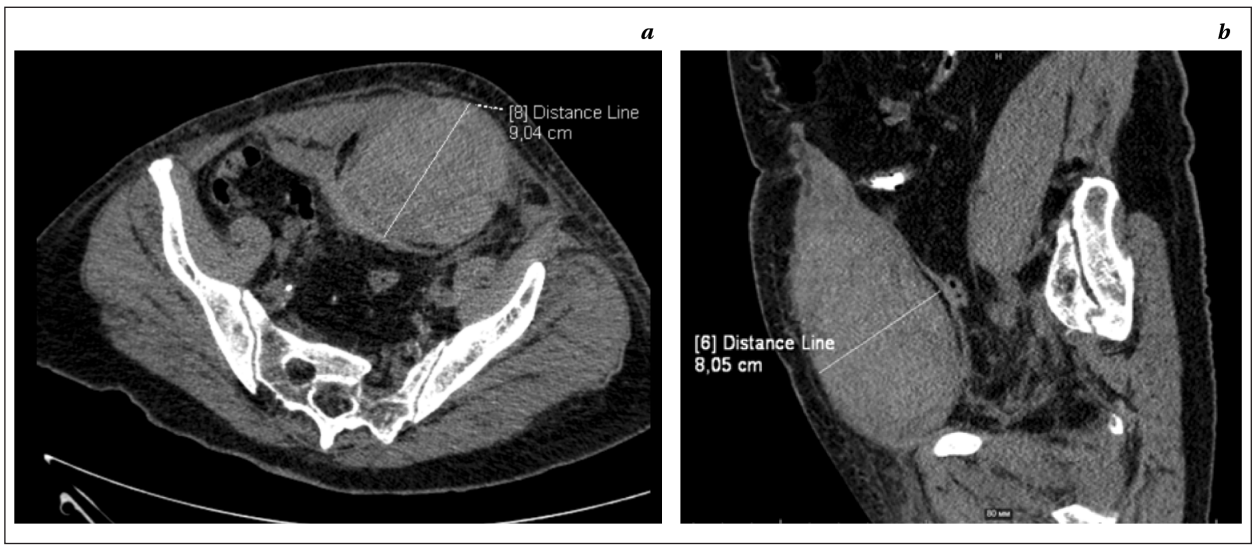

Fig. 1. Anterior abdominal wall hematoma: axial section (*a*), sagittal section (*b*). Patient T. (clinical case 1).

Clinical case 1

Patient T., male, 61 years old, hospitalized on day 12 from the onset of the disease. Patient's weight was 75 kg, height was 168 cm (BMI 26.6). On admission to the hospital, the patient had a positive RT-PCR for SARS-CoV-2 RNA. On chest CT scan the total pulmonary involvement was 76% (CT grade 3 according to the semi-quantitative visual assessment scale), respiratory rate was 24 per minute, SpO_2 was 70% on ambient air. The patient was admitted to the intensive care unit immediately from the emergency department. On day 2 after admission the noninvasive lung ventilation (NILV) was started, which continued for 8 days, and then high-flow oxygen therapy through nasal cannulas was administered for 4 days. To control agitation and prevent SILI (self-inflicted lung injury), the patient received fentanyl by microinfusion at the rate of 0.5–0.6 μg/kg/h in combination with dexmedetomidine 0.3 μg/kg/h during 8 days of NILV. This regimen allowed maintaining a sedation level of -2 to -1 on the RASS scale and 2 to 3 on the Ramsay scale. The patient received anti-inflammatory (glucocorticoids), antihypoxic (cytoflavin), gastroprotective, anticoagulant, fluid therapy, and mucolytics. The patient was in prone position most of the day. On day 23 from the onset (day 11 of hospitalization), the patient complained of severe pain in the left iliac and suprapubic region. The pain worsened with coughing and straining (the patient had constipation, medication therapy and enemas were used). On ultrasonic examination of the abdomen, a nonhomogenous cylindrical mass 160×70 (max) mm with clear, rather straight outlines was revealed in the left iliac region 2–8 mm deep. On chest CT anterior abdominal wall hematoma 350 ml in volume was found (Fig.1, *a* and *b*). A decrease in Hb from 142 to 125 g/l was also noted. After consultation with a surgeon, watchful waiting with conservative management strategy was chosen. Follow-up abdominal CT and soft tissue ultrasound examination 4 and 12 hours after initial investigations showed no change in the size of the mass and no signs of active bleeding.

However, taking into account the persistent pain and the risk of hematoma expansion, surgical intervention was performed on day 3 after hematoma detection which included dissection, revision, hemostasis and drainage. Under general anesthesia a 12 cm long pararectal incision on the left side was made, the skin, subcutaneous fatty tissue, the anterior wall of the sheath of rectus abdominis muscle were dissected. On opening the sheath, the hematoma 300 ml in volume containing clots was revealed. The clots were removed. The rectus abdominis muscle was partially disintegrated with frayed fibers and blood seeping from the muscle. Hemostasis using electrocoagulation and suturing was performed. The wound was sutured in layers. Aseptic dressing was applied. Postoperative drain was removed on day 2 after the surgery. Transfusion of 2 units of packed red blood cells and one unit of fresh frozen plasma (FFP) was done. The patient was transferred to the specialized department. On day 35 of hospitalization the patient was discharged with improvement.

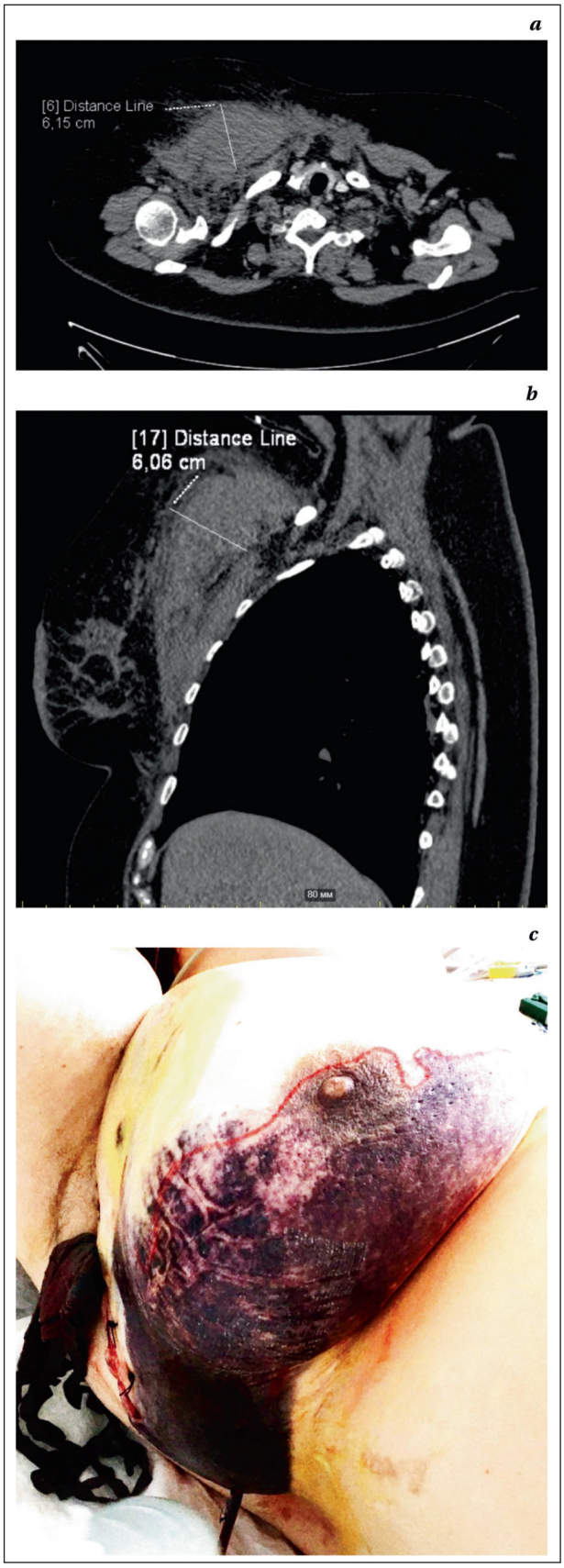

Fig. 2. Subpectoral hematoma: axial section (*a*), sagittal section (*b*) and soft tissue hematoma in the breast area (*c*). Patient M. (clinical case 2).

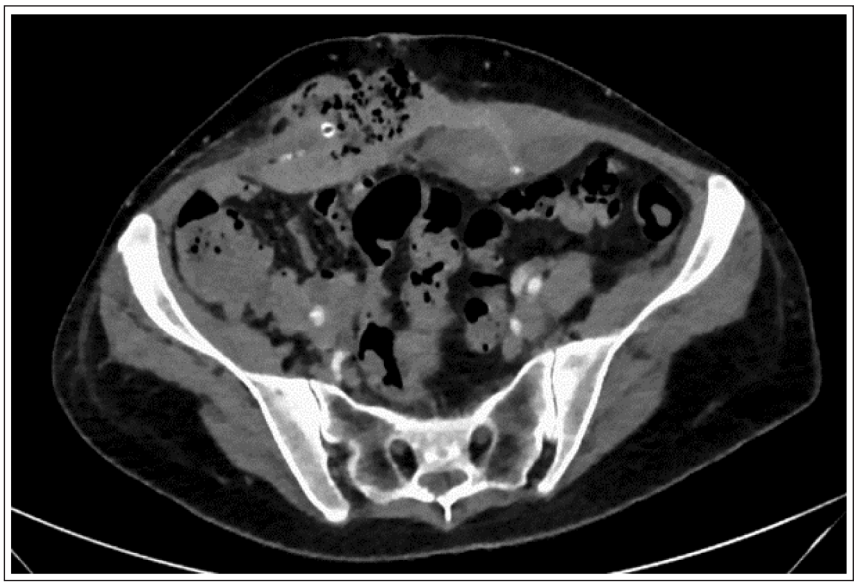

Fig. 3. Hematoma of the anterior abdominal wall, axial section. Patient B. (clinical case 3).

From the first day of admission the patient received anticoagulant therapy with nadroparin calcium 0.6 ml twice a day, on the day of surgery the anticoagulant was discontinued, the next day after surgery the therapy was resumed in a dose of 0.4 ml twice a day, starting from the 4th day — 0.6 ml twice a day. This strategy was chosen due to high risk of thrombosis and absent clinical and laboratory signs of hypocoagulation.

Clinical case 2

Patient M., female, 63 years old, was admitted to hospital with bilateral viral pneumonia. Weight 108 kg, height 157 cm (BMI 43.8). Her comorbidities included 3rd degree obesity and chronic kidney disease. Repeated RT-PCR of oropharyngeal swab specimens was negative for SARS-CoV-2. On day 11 from the disease onset, she was admitted to an infectious diseases ward. On admission, chest CT showed 80% lung involvement (CT grade 4 according to the semiquantitative visual assessment scale). On day 14 (day 3 of admission) she was transferred to the ICU due to progressive respiratory failure. After 7 days of high-flow oxygenation and intensive therapy, the patient stabilized, and the lung involvement decreased down to 60% according to chest CT. Glucocorticoids, antibacterial drugs (for 5 days), combination antihypertensive, anticoagulant (therapeutic dosage) therapy were administered, additionally, the patient received mucolytics.

On day 22 she was transferred to the general ward. On day 28 from the onset of the disease (day 17 from admission to the hospital) persistent hypotension was observed. Laboratory examination revealed reduced hemoglobin and hematocrit (initial Hb 100.0 g/l and Ht 27.9 dropped to Hb 84 g/l, Ht 24). On chest CT, right subpectoral hematoma (6.5×12×15.5 cm) was found (Fig. 2, *a–c*). Surgical intervention was performed urgently and included revision, debridement, and wound packing. Skin and subcutaneous tissue were dissected with a 12 cm incision in the lateral thoracic region. The subcutaneous tissue was soaked with blood. The spaces below the mammary gland, between the pectoralis major and minor muscles, and below the small pectoral muscle was separated. 500 ml of liquid blood and clots were evacuated. The wound was drained, diffuse blood oozing from the muscles was noted, and visible sources of bleeding were coagulated. Despite coagulation, sluggish diffuse blood seeping was observed. Packing of all previously separated spaces was performed using 3 45×45 cm surgical sponges. Active Redon drainage was placed under the mammary gland. The wound was loosely sutured. In the early postoperative period, a total of 5 units of FFP and 4 units of packed RBCs were transfused.

Later the patient was transferred to the surgical department, the wound was drained with a VAC system on day 17 after surgery, the patient was discharged on day 30 after surgery (day 47 from admission).

Clinical case 3

Patient B., female, 58 years old, was hospitalized on day 9 from the onset of the disease in the infectious disease unit. On admission, the chest CT showed 54% lung involvement. SARS-CoV-2 RT-PCR was positive. The patient's weight was 55 kg, height was 168 cm (BMI 19.49). Comorbidities included varicose veins of the lower extremities. Anti-inflammatory (steroid) and anticoagulant (therapeutic dosage) therapy was started. Due to severe systemic inflammatory response and evidence of «cytokine storm», olokizumab was prescribed with a positive effect.

On day 4 of hospitalization, the patient felt sharp pain in the left iliac region. Examination of the hypogastrium revealed a hematoma about 9×5 cm in size. Laboratory tests showed Hb decrease from 140 to 105 g/l. On chest CT, a hematoma 54×29×104 mm of the anterior abdominal wall in the left rectus abdominis muscle region was found (Fig. 3). Emergency surgical intervention was performed which consisted of dissection, debridement, and drainage of the

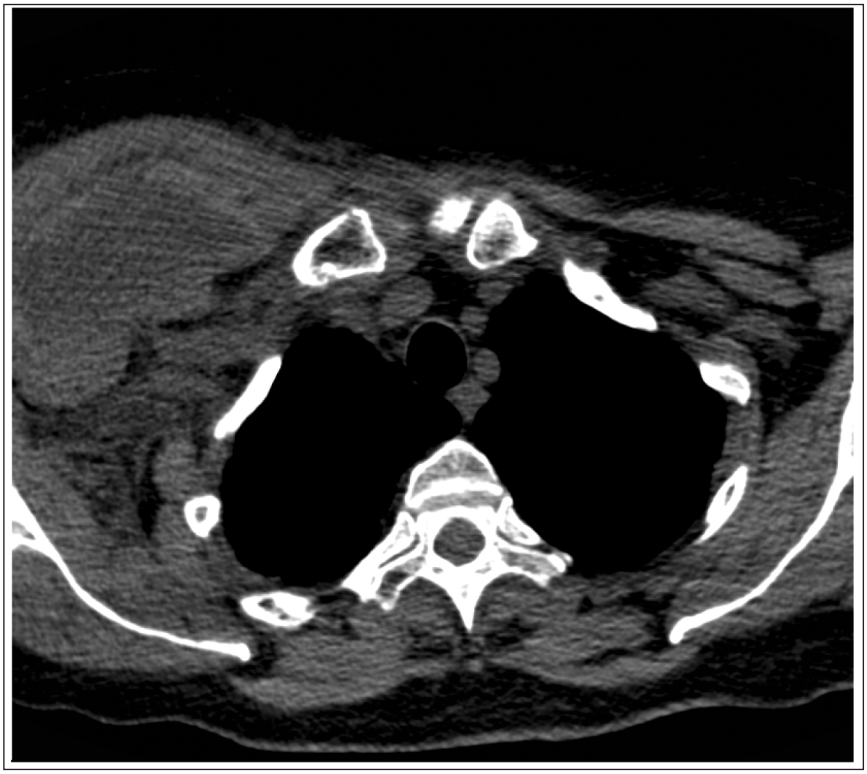

Fig. 4. Subpectoral hematoma. Patient T. (clinical case 4).

hematoma of the anterior abdominal wall. The hematoma of the left rectus abdominis muscle 20×15 cm in size was opened along the linea alba below the umbilicus. About 400–500 ml of liquid blood was released. The rectus abdominis muscle was soaked with blood. In the middle third of the muscle, a vessel of less than 1 mm was identified amid the muscle, which was the source of active bleeding. The vessel was sutured. Hemostasis was achieved. Aponeurosis and skin were sutured. Intraoperative transfusion of 1 unit of packed RBCs and 2 units of FFP was performed. In the early postoperative period, 600 ml of hemorrhagic discharge was drained. Subsequently, repeated surgical interventions were performed three times (6 hours after the first surgical intervention, on day 6 and 8) for surgical revision of hematoma, stopping the bleeding, and packing the rectus abdominis muscles. Anticoagulant therapy was adjusted: LMWH was withheld for the first two days after the bleeding, and then, due to the high risk of thrombotic complications, it was restarted in a prophylactic regimen. The total volume of transfusions during the treatment was 7 units of FFP, 7 units of packed red blood cells. The patient's condition was stable thereafter, treatment continued in the specialized ward. The wound healed by secondary intention. On day 36 the patient was discharged.

Clinical case 4

Patient T., female, 73 years old, was admitted to the infectious disease department on day 10 from the onset of disease. Chest CT revealed 70% of lung involvement (CT grade 3 according to the semi-quantitative visual assessment scale). RT-PCR for SARS-CoV-2 was positive. The patient's weight was 60.0 kg, height was 154 cm (BMI 25.3). The patient received anti-inflammatory (glucocorticoids), gastroprotective, anticoagulant therapy (in therapeutic regimen), and mucolytics. On day 21, follow-up chest CT scan revealed a fluid-containing abnormal mass located under the right pectoralis major and extending into the retro-mammary space 103×47×139 mm in size (Fig. 4). On the following day the subcutaneous hematoma increased to 128×81×156 mm. On palpation the mass was hard and protruding from under the lateral edge of the pectoralis major muscle. Patient's hemoglobin dropped from 123 to 87 g/L. Surgery was performed and included dissection, debridement, stopping the bleeding, and drainage. The skin and subcutaneous fatty tissue were dissected along the right anterior axillary line. The hematoma was dissected, 450 ml of lysed blood with clots was evacuated. The source of active bleeding was not identified. The surrounding tissues were markedly soaked with blood, scattered areas of active bleeding were spotted and coagulated. Two units of packed red blood cells were transfused. The postoperative period was uneventful. Anticoagulant therapy was withheld on the first day after surgery, then it was resumed in prophylactic regimen. The drainage was removed on the 2nd day. On day 29, the patient was discharged.

Clinical case 5

Patient T., male, 74 years old, was admitted to the intensive care unit on day 10 from the onset of the disease. RT-PCR for SARS-CoV-2 was positive. The chest CT showed that lung involvement was 80% (CT IV according to the semi-quantitative visual assessment system). Pa-

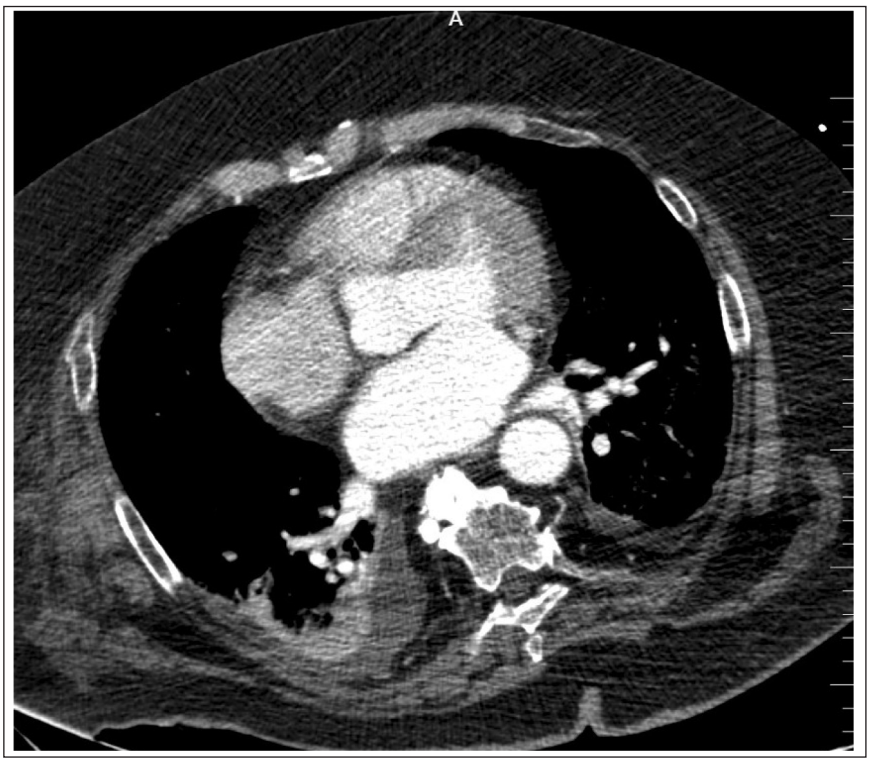

Fig. 5. Soft tissues of the lumbar area soaked with blood and hematoma in the psoas major muscle. Patient T. (clinical case 5).

tient's weight was 120 kg, height was 173 cm (BMI 40.09). Hypertension, chronic heart failure, rapid atrial fibrillation, 3rd degree obesity, and linea alba abdominal hernia were among comorbidities.

Before admission, the patient had been taking warfarin 5 mg continuously for a long time. The following coagulation test results were obtained on admission: APTT 47.8 s, prothrombin time 38.4 s, prothrombin (according to Quick) 18.00%, INR 3.40. Warfarin was discontinued due to the prescription of LMWH in a therapeutic dosage. On days 3 and 4 of hospitalization, due to progressive consumption coagulopathy (evidenced by further decrease in fibrinogen, increase in INR, and prolongation of prothrombin time) the dosage of LMWH was adjusted and transfusion of FFP was performed. Intensive therapy included anti-inflammatory (glucocorticoids), anticoagulant, antihypoxant, antihypertensive, antibacterial medications (both for bacterial superinfection of lungs and urinary tract infection). Propofol sedation was administered to relieve psychomotor agitation and discontinued after selection of neuroleptic drug. The patient received high-flow oxygen therapy for 16 days. Considering obesity and large umbilical hernia, the prone position was not easy to maintain, the patient was mostly in the lateral and supine position.

On day 21 of hospitalization, examination revealed a hematoma in the right lumbar region (Fig. 5). There were no complaints. Chest CT scan demonstrated hematoma in the right psoas muscle 110×50×45 in size. There was no evidence of extravasation. Consulting surgeon recommended conservative management. Follow-up CT (on days 17 and 26 from the hematoma formation) showed hematoma without worsening, its size was 115×56×52 mm. The right kidney and ureter were displaced laterally due to expansion of the right psoas muscle. Renal excretory function was intact. Serial CT and ultrasound examinations indicated stable size of hematoma with signs of lysis. The size of subcutaneous hematoma increased, but there was no damage to the skin integrity. Transient hematuria was noted. Anticoagulation was adjusted according to the results of coagulation tests and withheld for a short period of time if needed. On day 57 of hospitalization the patient was discharged.

Results

We analyzed possible risk factors for intramuscular hematomas. In all five clinical cases described, hematomas occurred with underlying anticoagulant therapy with LMWH administered in therapeutic doses due the high risk of thromboembolic complications. In patient from case 1 we initially considered possible link of hematoma with the technique of LMWH injection (into the anterior abdominal wall), but this hypothesis was rejected due to the deep localization of hematoma.

The data presented in Table show that intramuscular hematomas occurred with normal values of the routine coagulation tests, only in patient 5 a prolonged APTT was revealed. We should note that the measurement of individual coagulation factors was not performed due to technical reasons. The

Coagulation test results and platelet counts in patients at the moment of diagnosis of hematoma.

Test values	Values				
Patient	1	2	3	4	5
Prothrombin time, s	12.8	12.1	11.2	10.2	14.2
Prothrombin, %	84	93	106	129	86
INR	1.1	1.04	0.96	0.87	1.09
APTT, s	27.7	36.9	24,5	19.5	45.8
Fibrinogen, g/l	3.57	2.20	2.15	3.55	3.15
D-dimer, ng/ml	1798	511	1840	887	1730
Platelet count, $\times 10^9$/l	223	253	315	199	114

direct anticoagulants enoxaparin and nadroparin are known to block the Xa and IIa factors. The use of anti-Xa activity to monitor the therapeutic effect of LMWH in patients with COVID-19 seems more reasonable, as it reduces the risks of hemorrhagic complications [2, 4]. However, this test is performed in a limited number of laboratories and is relatively expensive compared to routine coagulation tests. Platelet count was also in normal range in all patients. Notably, patients with novel coronavirus infection are generally characterized by a decreased platelet count, which does not manifest clinically in most cases.

Apparently, the localization of hematomas was to some extent due to positional factors coupled with muscle strain in particular area. The subpectoral hematomas may have been precipitated by turning laterally. Interestingly, subpectoral hematomas were found only in women which is consistent with the other observations found in the literature [14]. The loss of blood vessel elasticity and lack of muscle elasticity, which are more commonly observed in the elderly, have also been reported in the literature as risk factors for hematoma development [14].

All patients had no other hemorrhagic complications, only the patient from case 5 had transient macrohematuria. In all cases the development of hematomas was clinically significant and accompanied by hypotension and severe anemia requiring blood transfusion. Surgical treatment of hematomas was indicated in 4 cases, moreover, repeated surgical interventions were required in 2 cases. All surgeries were performed under general anesthesia, with tracheal intubation and mechanical ventilation. Fentanyl or ketamine as well as propofol were used at the induction and anesthesia maintenance stage; rocuronium was used as a muscle relaxant. Despite severe viral lung injury there was no need in prolonged lung ventilation in postoperative period, all patients were extubated at the end of surgery, blood acid-base status remained stable, respiratory failure did not progress, and the oxygen therapy through nasal cannulas was continued in the postoperative period. Active drains were left in the wound in the postoperative period, otherwise wound packing was used, followed by stepwise removal of internal dressing.

Conclusion

Intramuscular and subcutaneous hematomas are uncommon but severe complications of coronavirus infection in patients receiving LMWH at therapeutic doses. High index of suspicion should be maintained in patients with COVID-19 regarding the risks of hemorrhagic complications. Physical examination and serial assessment of hemoglobin and hematocrit changes are crucial for the timely diagnosis of hematomas. Best strategies for anticoagulation in patients with coronavirus infection and high risk of VTE, as well as laboratory monitoring of LMWH use are yet to be explored.

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Risk Factors of Severe Disease and Methods for Clinical Outcome Prediction in Patients with COVID-19 (Review)

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Факторы риска и методы прогнозирования клинического исхода COVID-19 (обзор)

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Summary

Large population studies using statistical analysis and mathematical computer modeling could be an effective tool in studying COVID-19. The use of prognostic scales developed using correlation of changes in clinical and laboratory parameters and morphological data, can help in early prediction of disease progression and identification of patients with high risk of unfavorable outcome.

Aim of the review. To assess the risk factors for severe course and unfavorable outcome of COVID-19 and to evaluate the existing tools for predicting the course and outcome of the novel coronavirus infection.

PubMed, Medline, and Google Scholar were searched for the relevant sources.

This review contains information on existing tools for assessing the prognosis and outcome of the disease, along with the brief data on the etiology, pathogenesis of the novel coronavirus infection and the known epidemiological, clinical and laboratory factors affecting its course.

Conclusion. It is essential to develop predictive models tailored to specific settings and capable of continuous monitoring of the situation and making the necessary adjustments. The discovery of new and more sensitive early markers and developing marker-based predictive assessment tools could significantly impact improving the outcomes of COVID-19.

Keywords: COVID-19; risk factors; prognostic tools

Conflict of interest. The authors declare no conflict of interest.

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Introduction

The COVID-19 pandemic is a global problem affecting many aspects of social life. It has already caused enormous social and economic damage, and according to WHO, several waves of increasing morbidity worldwide are predicted [1]. Studying the clinical and epidemiological features of the disease and its pathogenesis could help better predict the outcomes of the infection and develop effective measures for its prevention and treatment.

The causative agent of infection is SARS-CoV-2 RNA virus of the Betacoronavirus genus. SARS-CoV-2 has multiple target cells in the human body and there are several clinical phenotypes of the disease. In most cases, the disease presents as an acute respiratory infection and/or mild to moderate pneumonia, but in some patients the virus infection leads to the development of ARDS, disseminated intravascular coagulation syndrome, and multiple organ failure. The reason for various clinical variants of disease lies in the genetic variability of SARS-CoV-2, individual characteristics of the patient's response to the infection, initial patient's status and many other factors affecting the pathological process.

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The use of prognostic scales based on correlation between changes in clinical and laboratory parameters and morphology can help in timely prediction of disease severity and selection of patients at high risk of unfavorable outcome.

The aim of this review was to assess risk factors for severe disease and adverse outcome of COVID-19, as well as current tools for predicting severity and outcome of novel coronavirus infection.

Sources were searched in PubMed, Medline, and Google Scholar databases. Key words searched were: «COVID-19», «SARS-CoV-2», «Betacoronavirus», «COVID-19 risk factors», «COVID-19 comorbidities», «COVID-19 prognosis», «COVID-19 outcome prognosis», «COVID-19 ICU», «mortality», «death». Of the more than 300 initially selected literature sources, 80 were included in the review, of them 78 sources were published within the last two years (2020–2021).

Targets and Manifestations of Viral Damage

The key factors influencing the severity of COVID-19 are the viral load and the characteristics of the patient's immune response [2]. Systemic inflammatory response of the body leading to organ damage plays the main role in the pathogenesis. Myocarditis [3–5], disorders of lungs [6], liver [7–9], kidneys [10, 11], nervous system [12, 13], skin [14–16] and other organs resulting from viral and/or autoimmune damage have been described in literature. Severe coronavirus infection is associated with the development of DIC with generalized endotheliitis [2] and multiple organ failure.

Lung damage manifested as pneumonia (in some cases associated with ARDS) is most common in COVID-19. In SARS-CoV-2 ARDS, as in ARDS of other etiologies [17, 18], several subtypes, hypo- and hyperinflammatory, were identified [19]. In a prospective observational study by Sinha P. et al. [20], the hyperinflammatory subtype was characterized by higher values of ferritin, lactate dehydrogenase (LDH), and mortality, although the differences in these parameters were not significant due to the small sample size (only 39 patients).

Pathological examination of pulmonary tissue of patients who died from COVID-19 revealed diffuse alveolar damage, microcirculatory disturbances, thrombosis of pulmonary artery branches [21]. High cytokine blood concentration during disease correlated with elevated levels of pyroptosis and apoptosis on post-mortem microscopic examination [22].

Risk Factors

This review outlines the risk factors studied in patient populations only with a confirmed diagnosis of COVID-19 by detecting RNA or viral proteins in patient tissues *in vivo* or during pathological examination.

Given the possible heterogeneity of patient populations and different predominant factors in each of them, there are studies investigating both the general patient population [23] and separately populations of patients treated in the intensive care unit [24], patients with cancer [25], asthma [26], diabetes mellitus [27], obesity [28], and elderly [29] and pediatric patients [30]. In most studies, the groups consisted of non-survivors. The factors influencing admission to hospital [31] or ICU [32], as well as the need for mechanical lung ventilation [33] were also evaluated.

The main factors increasing the risk of mortality in the general population were various comorbidities, such as diabetes mellitus, obesity, hypertension, chronic heart, lung, liver, kidney diseases, and dementia. These factors have been identified from several meta-analyses and retrospective studies, the largest sample being 20,133 patients [34–37]. Several retrospective studies had shown that Charlson comorbidity index, which correlated well with mortality in the general population of patients with COVID-19, could be an integral tool for assessing comorbidities and their severity [38–40]. Male gender was associated with an increased risk of death in most studies [41]. Although an older age has been considered a risk factor for complicated COVID-19 in numerous studies [42–44], in a meta-analysis Starke K. et al. [45] have reported that age is a confounder but not an independent mortality risk factor. With advancing age the comorbidities are naturally increasing that contribute to the development of severe disease.

Among the parameters assessed in patients with confirmed novel coronavirus infection on hospital admission, mortality was significantly affected by the following (based on several retrospective cohort studies and meta-analyses, involving from 63 to 16100 patients): extent of lung involvement on CT [46, 47], elevated D-dimer [48] level, leukocytosis, leukopenia [49], low platelet count [50], high C-reactive protein (CRP) [51], LDH [52], ferritin [53], low CD4 and CD8 cell counts [49].

Treatment and observation in the ICU were required in 6–32.3% of cases [44, 41, 54, 55]. Patients treated in the intensive care unit are a special population that should be examined separately. The patients in the ICU are closely and regularly monitored, and the range of parameters measured is often much broader.

As in the general population, various chronic comorbidities in the ICU patients significantly influenced mortality. Male gender and older age were also associated with increased mortality in COVID-19 [24].

Lung injury with the development of ARDS-like syndrome was the main reason for ICU admission for respiratory support. An extremely low oxygenation index (PaO_2/FiO_2) on admission to ICU, mostly less than 100, as well as high alveolar-arterial difference were significant factors increasing mortality [24, 54, 55]. Mechanical lung ventilation per se was not a factor associated with mortality [56]. There are studies describing phenotypes of lung injury in patients with COVID-19 on mechanical ventilation [57, 58]. The presence of atelectasis, low pulmonary compliance and reduced alveolar recruitment are attributed to advanced lung damage, and this phenotype is considered to be more severe. Elevation of PEEP necessary to increase gas exchange area leads to the elevated risk of barotrauma [59, 60]. Grasselli G. et al. [61] demonstrated association between high PEEP and increased mortality.

Plasma levels of interleukin-6 (IL-6), IL-1, IL-8, tumor necrosis factor-alpha, interferon-gamma, and alpha1-antitrypsin were elevated in ICU patients who developed organ dysfunction [62]. High IL-6 and low alpha1-antitrypsin were related to an increased risk of death [62].

The hypothesis of SARS CoV 2-associated endotheliitis development was confirmed by a significant increase in endothelial damage markers in patients with severe disease. Goshua G. et al. [63] showed a significant difference in plasma levels of von Willebrand factor, P-selectin and thrombomodulin in ICU patients compared to non-ICU patients. High levels of the above markers were associated with increased mortality.

Prognostic tools. The need to rapidly and accurately assess the patient's condition and predict the outcome of the disease prompted researchers to create prognostic tools. In the early period of the epidemic, patients were assessed using the existing qSOFA, APACHE II, PSI, SMART-COP, CURB-65, MuLBSTA, NEWS scales [64]. A study by Garcia-Clemente M. [65] showed that PSI and CURB-65 scales were the most accurate in predicting death in patients with SARS-CoV-2-induced pneumonia. Other researchers [66] showed the applicability of previously developed Clinical Frailty Scale (CFS) to assess the risk of fatal outcome and mechanical ventilation. Jang J. et al. [67] demonstrated the advantage of NEWS scale over qSOFA and SIRS scales to assess risk of ICU hospitalization and 28-day mortality. Kostakis I. et al. [68] recommend using the NEWS and NEWS2 scales to assess the risk of clinical deterioration in patients with COVID-19.

Later on, the growing body of evidence has led to creation of specific scales. In the largest study by Knight S. et al. [69], which included 35,463 patients from the general population, 8 variables (age, sex, number of comorbidities, respiratory rate, SpO_2, level of consciousness, levels of urea, C-reactive protein) affecting mortality were identified (AUC=0.79 with 95%CI, 0.78–0.79).

Another study [70] included 1590 patients from the general population who had severe disease, i.e., hospitalization in ICU, the need for mechanical ventilation or fatal outcome. The created scale included 10 parameters (chest radiographic abnormality, age, history of lung bleeding, dyspnea, level of consciousness, number of comorbidities, presence of cancer, neutrophil-to-lymphocyte ratio, LDH, direct bilirubin) with AUC=0.88, CI: 0.85–0.91. Covino M. et al. [71], comparing various predicting tools, reported the above-mentioned scales [69, 70] as the most accurate.

Yuan Y. et al. [72] evaluated several dozens of risk factors of poor prognosis and selected three most significant ones including LDH level, CRP concentration, and lymphocyte percentage. These parameters were included in a validated prognostic scale that allows to stratify all the admitted patients into three risk groups. A total of 1,479 patients from the general population participated in the study. The authors report sensitivity of over 90% with AUC=0.96.

In a similar study [73] based on the data of 2529 patients, the authors proposed a prognostic scale allowing to classify the admitted patients into high and low risk groups. The scale included such parameters as age, history of chronic coronary heart disease, D-dimer, procalcitonin and percentage of lymphocytes (AUC 0.92; *P*=0.26).

A. Vaid et al. [74] used machine learning to develop a model predicting the probability of fatal outcome or a critical event (tracheal intubation, ICU admission, transfer to hospice) on days 3, 5, 7, 10. Clinical and laboratory data from 3715 patients obtained within the first 36 hours of hospitalization were used for training, and the model was validated on 383 patients. The most significant drivers for critical event prediction were acute kidney injury, LDH level, respiratory rate, glucose level (both high and low), systolic and diastolic blood pressure, blood pH value, total protein, CRP, and D-dimer level. Age, anion gap, CRP, LDH, SpO_2, urea, ferritin, lactate, red blood cell distribution width, and diastolic pressure were important for prediction of mortality.

G. Wu et al. [75] used data from 725 patients to develop a model predicting the risk of extremely severe course of COVID-19 for groups of symptomatic and asymptomatic patients, both with positive PCR test. If laboratory results and a lung CT scan were available, these data were also added. Parameters used in the model included age, hospital employment (working with COVID-19 patients), body temperature, time of onset to admission, chest CT lesion range, percentage of lymphocytes, and blood levels of CRP, LDH, urea, creatine kinase, and total calcium. The AUC increased from 0.74 to 0.86 since more patient data became available).

In a study [76], the authors developed a mortality risk assessment scale on days 7 and 14. The study used data from 931 patients. Statistical analysis was used to select 4 most significant clinical and laboratory parameters such as age, mean blood pressure, kidney injury (stage 2 or higher according to KDIGO AKI), and severe hypoxia (SpO_2 below 90%, respiratory support more than 4 liters of oxygen per minute, noninvasive/invasive lung ventilation). The AUC was 0.86 for 7-day mortality and 0.83 for 14-day mortality. When validated using data from 265 patients, the AUC for 7- and 14-day mortality assessments was 0.85 and 0.83, respectively.

Jiao G. et al. [77] proposed a nomogram determining the risk of extremely severe disease based on 7 parameters: age, LDH, CRP, direct bilirubin, albumin, urea levels, and RBC distribution width. The study involved 372 patients, sensitivity of the nomogram was 85.7%, specificity was 87.6%.

Haimovich A. et al. [78] developed a simple scale to assess the probability of respiratory failure in the next 24 hours. The study involved 1,172 patients. The scale included only three parameters: respiratory rate, SpO_2 and inhaled oxygen flow with AUC=0.81, CI: 0.73–0.89.

The team of Zhang C. et al. [79], using the parameters of 80 patients, developed a prognostic scale to assess the risk of invasive ventilation and death. The scale included patient age, white blood cell count, neutrophil count, glomerular filtration rate, and myoglobin level. The researchers reported 70.8% sensitivity and 89.3% specificity of prognosis made using this scale.

Prognostic tools are a good aid to the attending physician in making care decisions. Currently, based on statistical analysis and machine learning, a large number of prognostic scales, nomograms, and computer models have been developed around the world that allow predicting the outcome with varying accuracy. However, it is unclear whether these models are universal. Futoma J. and Simons M. believe that prognostic tools should be used in specific places, at specific times, and in specific patient populations, giving the ever-changing treatment guidelines, differences in resources between health care systems, demographic, phenotypic, genetic characteristics of patient populations, etc. as a rationale [80]. This suggests the need to develop prognostic models tailored to specific circumstances, with continuous monitoring of the situation and necessary adjustments.

Unfortunately, many factors that significantly correlate with an adverse outcome are markers of both existing organ damage and organ failure.

Conclusion

There is a need to develop prognostic models tailored to specific circumstances with continuous monitoring of the situation and the possibility of making adjustments if necessary. The discovery of new markers that are more sensitive in the early stages of the disease and developing biomarker-based prognostic tools could significantly improve the outcomes of COVID-19.

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Dexamethasone and SARS-CoV-2: the Dangerous Steroids Pandemic (Letter to the Editorial Office)

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Дексаметазон и SARS-CoV-2: опасная пандемия применения стероидов (письмо в редакцию)

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As of August 4, 2021 severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2) has so far caused 4,235,559 deaths [1]. The most serious coronavirus disease 2019 (COVID-19) cases develop a life-threatening hyperinflammatory response to the virus with massive release of pro-inflammatory cytokines. Many efforts have been sustained to find a suitable therapy for this new disease.

Given the lack of a proven antiviral therapy, various immunosuppressive agents have been tested with the aim to reduce the hyperinflammatory state associated with COVID-19 and therefore improve patient prognosis. The RECOVERY trial [2], reported the beneficial effect 6 mg dexamethasone administration for ten days once a day in COVID-19 patients. The incidence of death in the dexamethasone group compared with the control group was 23.3% vs 26.2% for patients receiving oxygen, and 29.3% vs 41.4% for patients on mechanical ventilation at the time of randomization.

However, the study was not blinded. This is relevant as blinded trials appear to generally have a 40% higher number-needed-to-treat as compared with open-label studies [3]. Notably, three out of five randomized clinical trials analysing corticosteroids administration in COVID-19 patients published so far including the RECOVERY trial, were open label. Therefore, we posit that effect size for corticosteroid use in COVID-19 is probably overestimated.

Furthermore, while corticosteroids may reduce the hyperimmune response underlying the most severe cases of COVID-19, the immunosuppressive action of the drug is likely to promote the coinfections that characterize the course of many clinical cases.

Of note, even if the use of corticosteroids in hospitalized patients with severe forms of COVID-19 decreases mortality with a number needed to treat of 19, the use in SARS-CoV-2 infected persons with no indication may lead to a rise in mortality with a number needed to harm of 28 [4].

Unfortunately, the rate of people infected with SARS-CoV-2 with correct indications for corticosteroid use is significantly lower than the number of people without indications [5]. Nevertheless, there is currently a worldwide indiscriminate use of corticosteroids regardless of indications [6]. We therefore propose that considerable effort should be directed to the education of

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physicians to avoid an incorrect use of steroids, which although beneficial on a limited number of patients, can be harmful and lethal in most people infected by SARS-CoV-2.

Conflicts of interest. Authors declare no conflict of interest.

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Based on the **«Brief author guidelines for preparing and formatting scholarly papers in journals indexed in international scientific databases»** edited by Olga Kirillova under the ASEP (Association of Scientific Editors and Publishers) and RRIEPL (Russian Research Institute of Economics, Politics and Law in Science and Technology) published in 2019, **The CSE's White Paper on Promoting Integrity in Scientific Journal Publications**, 2012 Update, **ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals** (December 2016), and **The European Association of Scientific Editors (EASE) Guidelines for Authors and Translators** (available at **https://ease.org.uk/guidelines-toolkits/**).

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