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Original Article

Critically ill patients with COVID-19 in Tokyo, Japan: A single-center case series

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ABSTRACT

Introduction: We reported, in our previous study, a patient with coronavirus disease 2019 (COVID-19) who was successfully treated with extracorporeal membrane oxygenation. Data on clinical courses and outcomes of critically ill patients with COVID-19 in Japan are limited in the literature. This study aimed to describe the clinical courses and outcomes of critically ill patients with COVID-19 in Tokyo, Japan.
Methods: This is a single-center case series study. Patients with COVID-19 treated with mechanical ventilation (MV) were reviewed retrospectively. Data on baseline characteristics, in-hospital treatment, and outcomes were collected.
Results: Between February 2, 2020, and June 30, 2020, 14 critically ill patients with COVID-19 were treated with MV. Most patients were male and had comorbidities, especially hypertension or diabetes; 35.7% were overweight and 21.4% were obese. The majority of the patients had dyspnea on admission. The median duration of MV was 10.5 days, and the 28-day mortality rate was 35.7%. In the four patients with COVID-19 who died, the cause of death was respiratory failure.
Conclusions: As in previous reports from other countries, the mortality rate of patients with COVID-19 requiring intensive care remains high in Tokyo. Further study on the appropriate timing of MV initiation and specific treatments for critically ill patients with COVID-19 is needed.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since a cluster of initial cases was reported in December 2019 in Wuhan, China, cases of COVID-19 have been reported globally [1]. In Japan, the first laboratory-confirmed COVID-19 case was reported on January 14, 2020. Although the Japanese government declared a state of emergency on COVID-19 on April 7, 2020, the number of patients and deaths has increased. As of June 30, 2020, there had been 6225 confirmed cases and 320 deaths in Tokyo [2].

The severity of COVID-19 ranges from common cold to life-threatening pneumonia. In previous studies, the proportion of COVID-19 patients requiring intensive care ranged from 5% to 14.2% [3,4]. When limited to the intensive care unit (ICU) settings, the case fatality rate of COVID-19 ranged from 26% to 67% [5–8]. Data from China suggested that COVID-19 patients required a long period of mechanical ventilation (MV) [5]. The number of patients requiring intensive care has been increasing and is beginning to exceed regional capacity in Japan.

We previously reported a COVID-19 patient who was successfully treated with extracorporeal membrane oxygenation (ECMO)

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MV, mechanical ventilation; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; RT-PCR, reverse transcriptase polymerase chain reaction; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; PEEP, positive-end expiratory pressure; SD, standard deviation; IQR, interquartile range.

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[9]. However, there are limited data on clinical courses and outcomes of critically ill patients with COVID-19 in Japan. Healthcare workers have been required to manage COVID-19 cases without adequate clinical data. Our report aims to describe the demographic characteristics, clinical courses, and outcomes of critically ill patients with COVID-19 in Tokyo.

2. Patients and methods

2.1. Study design

This single-center case series study was conducted at Tokyo Metropolitan Bokutoh Hospital. Our institution is a tertiary emergency medical facility in eastern Tokyo and has a capacity of 765 beds, including 10 specialized beds to care for patients with highly contagious diseases.

2.2. Patients

In this study, we enrolled laboratory-confirmed COVID-19 patients aged ≥18 years and treated with MV in the ICU or an acute care bed because of acute respiratory distress syndrome (ARDS) from February 12, 2020, to June 30, 2020. Laboratory-confirmed COVID-19 was defined by a positive result of reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 from a nasopharyngeal swab or sputum specimen. ARDS was defined by the Berlin Definition [10]. Patients were excluded if they were under 18 years of age or had not received MV at their request (all these had a "do not attempt resuscitation" order on admission). All patients, excluding those with fatalities, were observed for more than 28 days.

2.3. Data collection

We collected data from electronic medical records on age, sex, nationality, body weight, body mass index (BMI), transmission route (community-acquired or hospital-acquired), and comorbidities (chronic cardiac disease, chronic obstructive pulmonary disease [COPD], interstitial lung disease, chronic kidney disease, hypertension, diabetes mellitus, malignancy, and smoking). Data on symptoms from onset to hospital admission (fever, fatigue, dry cough, expectoration, dyspnea, anorexia, myalgia, sore throat, diarrhea, and nausea), laboratory findings on admission (white blood cell count, absolute lymphocyte count, creatinine, aspartate transaminase, alanine transaminase, lactate dehydrogenase, C-reactive protein, D-dimer, hemoglobin A1c) were also obtained. Further, information on chest computed tomography (CT) findings on admission, in-hospital treatment (antibacterial agents, investigational antiviral agents, glucocorticoid, renal replacement therapy, neuromuscular blockade, prone position, and ECMO), characteristics of MV (highest positive-end expiratory pressure [PEEP], the worst ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [P/F]), symptomatic thrombotic complications, and clinical outcomes were included. Infection was defined as hospital-acquired if patients who were already hospitalized for other reasons for more than 48 h began to show COVID-19 symptoms.

2.4. IRB and analysis of clinical data

Study approval was obtained from the institutional ethical review board of the Tokyo Metropolitan Bokutoh Hospital. Informed consent was obtained through opt-out forms on the website. The first and last authors take complete responsibility for the integrity of the data and the accuracy of the data analysis. We used descriptive statistics. Data were expressed as mean, standard deviation (SD), median, or interquartile range (IQR) for continuous variables and number or percentage for categorical variables. Data were censored on June 30, 2020.

3. Results

3.1. Baseline characteristics

From February 20 to June 30, 2020, 14 laboratory-confirmed COVID-19 cases were admitted to our hospital and treated with MV because of ARDS. Baseline characteristics are shown in Table 1. The mean age was 59.9 years old (SD 12.7, range 39–80). Of all patients, 78.5% were male. All patients were Japanese. Five patients (35.7%) were overweight (BMI 25–29.9 kg/m^2) and 3 (21.4%) were obese (BMI ≥30 kg/m^2). The transmission route of SARS-CoV-2 was considered hospital-acquired in four cases (28.6%). The most common comorbidities were hypertension (57.1%), diabetes (50%), chronic cardiac disease (21.4%), COPD (14.2%), and chronic kidney disease (14.2%) in that order. On admission, dyspnea was found in all patients, fever and dry cough were observed in 13 (92.8%), fatigue in 12 (85.7%), and anorexia in 10 (71.4%).

3.2. Laboratory and radiographic findings

Laboratory findings and radiographic findings on admission are shown in Table 2. Leukopenia, mild liver dysfunction, and elevated C-reactive protein were common in these patients. The median absolute lymphocyte count was 790/μL (IQR: 591–945). Aspartate transaminase, alanine transaminase, and lactate dehydrogenase were one to two times the normal range. The median C-reactive protein was 11.5 mg/dL (IQR: 10–19.1).

Table 1
Baseline characteristics.

Characteristic	Total patients (n = 14)
Mean Age ± SD (range)	59.9 ± 12.7 (39–80)
Sex no. (%)	
Male	11 (78.5)
Female	3 (21.5)
Nationality no. (%)	
Japanese	14 (100)
Body weight median (IQR), kg	69.8 (65–81.5)
BMI median (IQR), kg/m^2	26 (24–27.6)
Transmission route no. (%)	
Community-acquired	10 (71.4)
Hospital-acquired	4 (28.6)
Comorbidity no. (%)	
Chronic cardiac disease	3 (21.4)
Chronic obstructive pulmonary disease	2 (14.2)
Interstitial lung disease	1 (7.1)
Chronic kidney disease	2 (14.2)
Chronic liver disease	0 (0)
Hypertension	8 (57.1)
Diabetes	7 (50.0)
Malignancy	1 (7.1)
Smoking	12 (85.7)
Symptoms no. (%)	
Dyspnea	14 (100)
Fever	13 (92.8)
Dry cough	13 (92.8)
Fatigue	12 (85.7)
Anorexia	10 (71.4)
Expectoration	6 (42.8)
Myalgia	2 (14.2)
Sore throat	1 (7.1)
Nausea	1 (7.1)
Dysgeusia	1 (7.1)
Diarrhea	0 (0)
Dysosmia	0 (0)

BMI: body mass index, IQR: interquartile range.

Of the 14 patients, 13 had a chest CT scan on admission. All patients had bilateral lung abnormalities. The main findings were ground-glass opacity (84.6%), consolidation (38.5%), and, in some cases, atelectasis (15.4%) and pleural effusion (15.4%). Only one patient had pneumothorax on admission.

3.3. Clinical course and outcome

The clinical courses of 14 patients are shown in Fig. 1. Median days from onset to admission were 9 days (IQR: 8–11). Three patients received MV with emergency intubation on admission day, and the others received MV after about 3 days (IQR: 2–4.5) of hospitalization. Median days of MV were 10.5 days (IQR: 8.25–13.5). During MV, the median of the highest PEEP was 12.5 cmH_2O (IQR: 12–16), and the median of the worst P/F ratio was 135 (IQR: 77–176). Of three patients treated with ECMO, two were discharged from the hospital, and one died while receiving ECMO. Symptomatic thrombotic complications were found in three patients; two had deep vein thrombosis and one had an ischemic stroke. As of June 30, 2020, 8 patients were discharged from the hospital, five had died, and one continued treatment in the hospital because of neurological sequelae. The 28-day mortality rate was 35.7%. Of the four patients with hospital-acquired infection, three were alive and discharged and one died. Respiratory failure was the cause of death for patients with COVID-19 who died.

3.4. In-hospital treatment

Details of in-hospital treatment and outcomes are shown in Table 3. During hospitalization, all patients were treated with antibacterial agents, 11 (78.8%) with antiviral agents (1 patient switched from lopinavir-ritonavir to favipiravir), two (14.2%) with glucocorticoid, two (14.2%) with renal replacement therapy, and two (14.2%) with ECMO.

4. Discussion

So far, there are few reports on the clinical course and outcome of critically ill patients with COVID-19 in Japan [11]. To describe the clinical courses and outcomes, we report on 14 critically ill patients with laboratory-confirmed COVID-19 in Tokyo. Eleven (78.5%) were admitted to ICU beds, and four were admitted to acute care setting beds because all ICU beds were already occupied. Male patients accounted for about 80%, more than half of the patients were overweight or obese, and most patients had comorbidities.

Table 2
Laboratory and radiographic findings on admission.

Laboratory findings	n = 14
White blood cell count,/μL	5200 (4400–7175)
Absolute lymphocyte count,/μL	790 (591–945)
Creatinine, mg/dL	1.0 (0.7–1.5)
Aspartate transaminase, U/L	45 (33–55)
Alanine transaminase, U/L	37 (27–49)
Lactate dehydrogenase, U/L	383 (321–513)
C-reactive protein, mg/dL	11.5 (10–19.1)
D-dimer, μg/mL	1.9 (1.4–3.7)
Hemoglobin A1c, %	6.7 (6.2–7.1)
Chest CT findings	**n = 13**
Bilateral	13 (100)
Ground-grass opacity	11 (84.6)
Consolidation	5 (38.5)
Cavitation	0 (0)
Atelectasis	2 (15.4)
Pleural effusion	2 (15.4)
Pneumothorax	1 (7.7)

Data are shown as median (IQR).
CT: computed tomography.

In our case series, all patients had dyspnea on admission regardless of the requirement for oxygen supply or MV. Other respiratory symptoms, like dry cough or expectoration, were also chief complaints. Only 1 of the 14 patients did not have a fever. A small proportion had gastrointestinal symptoms. In previous reports, including patients with mild illness, only approximately 20% of patients had dyspnea on admission [3]. Patients who complain of respiratory symptoms, especially dyspnea, on admission may be prone to later severe illness.

The mortality rate of critically ill patients with COVID-19 in our study (35.7%) is comparable to the lower range of the mortality rate in previous reports from China, the USA, and Italy (26–67%) [5–8]. There are several possible reasons why the mortality rate in Japan is lower. First, as of June 30, 2020, in Japan, all patients with laboratory-confirmed COVID-19 were hospitalized. Moreover, the number of coronavirus infections in Japan is lower than that in China, the USA, or Italy. This may lead to early detection of respiratory failure. Second, we thought about initiating MV in the early phase of respiratory failure. In patients with COVID-19, the progression of respiratory failure is very rapid. In our study, the median duration from receiving oxygen supply to receiving MV, high-flow nasal cannula (HFNC), or non-invasive positive-pressure ventilation (NPPV) was 3 days (IQR: 2–4.5). To avoid mistimed treatment, we considered starting MV management when peripheral capillary oxygen saturation (SpO_2) could not be maintained at more than 92% even with 5 L/min oxygen administration.

The duration of MV for COVID-19 is considered to be long as with other coronavirus infections [6]. As mentioned in a previous report, in the Middle East respiratory syndrome (MERS) cases, the median duration of MV was 16 days (range: 4–30) [12]. Our data show that the median duration of MV was 10.5 days (IQR: 8.25–13.5), which is comparable to the duration of MV in influenza A (H1N1) [13].

In our study, 11 of 14 patients received antiviral agents, and 2 of 14 critically ill COVID-19 patients received glucocorticoids. Antiviral agents that have activity against SARS-CoV-2 include remdesivir and favipiravir. Remdesivir has been reported to reduce the time to recovery in COVID-19 patients in a randomized controlled trial (RCT) [14]. In the subgroup analysis of this report, the effect was greater in patients who required supplementary oxygen and who did not receive MV. Favipiravir has been reported to accelerate viral clearance, but there are currently few reports of improved clinical outcomes [15]. In critically ill COVID-19 patients, glucocorticoid has shown improved 28-day mortality and should be administered [16]. However, the above RCT was reported after this study period, and glucocorticoids were not administered to our patients. Further reports on clinical outcomes of antiviral agents used in critically ill COVID-19 patients are desired.

A previous RCT has reported that prone positioning, in addition to low tidal volume ventilation, it reduces mortality in severe ARDS patients with P/F ratios below 150 [17]. Moreover, prone positioning has been reported to improve lung recruitability in COVID-19 patients [18]. However, the above RCT was conducted at facilities providing daily prone positioning for more than 5 years. The frequency of adverse effects was very low. We did not perform prone positioning because we had little experience in performing the procedure, and there were concerns about adverse effects due to staff skill and the number of staff. This may have affected mortality, but we believe that further study on the effectiveness of prone positioning in critically ill patients with COVID-19 is needed.

Some critically ill patients with COVID-19 were treated with ECMO [6,8,9], although the effectiveness in COVID-19 patients is unknown. In this case series, 3 of 14 patients were treated with

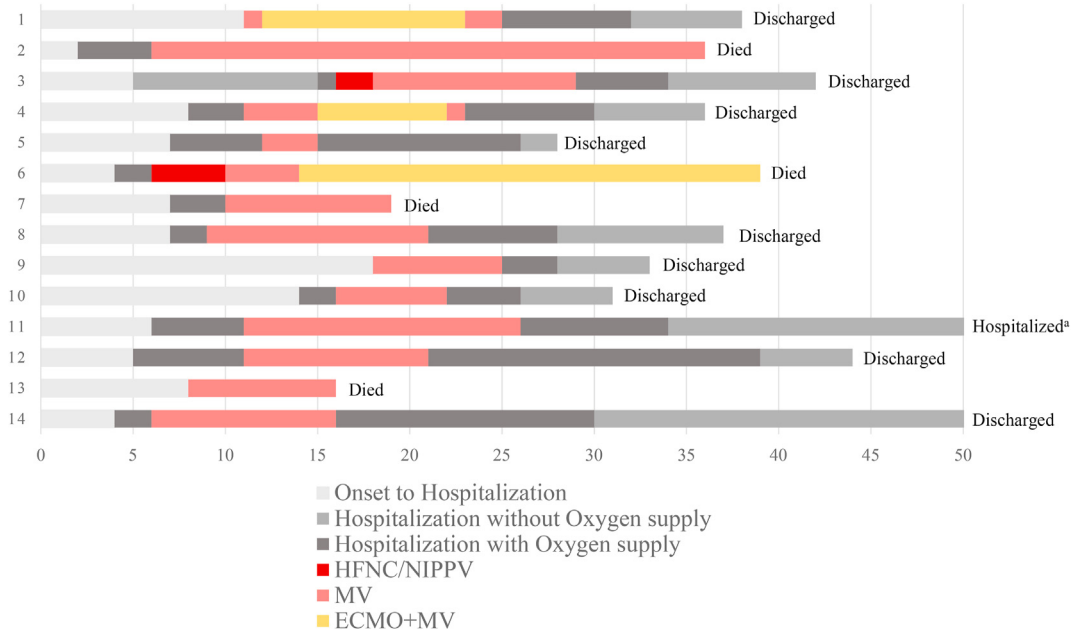

Fig. 1. Clinical course of critically ill patients. a: Patient 11 was still hospitalized because of neurological sequelae as of 91 hospital days. The vertical axis shows the patient number. The horizontal axis shows the number of days from the appearance of symptoms. As of June 30, 2020, 9 patients were discharged, 4 patients died, and 1 patient remained hospitalized. HFNC: high-flow nasal cannula, NIPPV: non-invasive positive-pressure ventilation, MV: mechanical ventilation, ECMO: extracorporeal membrane oxygenation.

Table 3
In-hospital therapies and outcomes.

	Total patients (n = 14)
Therapy	no. (%)
Antibacterial agents	14 (100)
Antiviral agents	
Lopinavir-ritonavir	3 (21.4)
Fabipiravir	8 (57.1)
Remdesivir	1 (7.1)
Glucocorticoid	2 (14.2)
Renal replacement therapy	2 (14.2)
Neuromuscular blockade	7 (50)
Prone position	0 (0)
Extracorporeal membrane oxygenation	2 (14.2)
Symptomatic thrombotic complications	no. (%)
Deep vein thrombosis	2 (14.2)
Cerebral infarction	1 (7.1)
Characteristics of MV	median (IQR)
the highest PEEP	12.5 (12–16)
the worst P/F ratio	135 (77–176)
Outcome	no. (%)
Discharged	7 (50)
Died	6 (42.8)
Hospitalized	1 (7.1)

As for the outcomes, information as of June 30, 2020, is shown.
MV: mechanical ventilation, PEEP: positive-end expiratory pressure, P/F ratio: the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, IQR: interquartile range.

ECMO: a 45-year-old man with hypertension and diabetes was discharged from the hospital, a 43-year-old man without underlying illness was discharged, and a 51-year-old woman with dyslipidemia, chronic kidney disease, and immunosuppression died. More clinical data are required to determine the eligibility of patients to be treated with ECMO.

Our study has some limitations. This is a single-center case series with a small number of patients, and we included only patients who received MV. Older patients with many comorbidities tended to have “do not attempt resuscitation” orders and did not receive MV. This tendency might lower the mortality rate.

In summary, the majority of critically ill patients with COVID-19 have comorbidities. Like previous reports from other countries, the mortality rate of COVID-19 patients requiring intensive care is still high in Tokyo, Japan. Further study on the appropriate timing of MV initiation and specific treatments for critically ill patients with COVID-19 is needed.

Ethics approval and consent to participate

The institutional review boards in Tokyo Metropolitan Bokutoh Hospital (trial registration: 02-032, registered on June 25, 2020) approved an opt-out method for obtaining informed consent.

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Authorship statement

All authors meet the International Committee of Medical Journal Editors (ICMJE) authorship criteria. SM wrote the manuscript. SM and NS revised and edited the manuscript. TW, AK, YK, TI, MH, TO, HK, SI, and FN critically revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript to be published.

Declaration of competing interest

None.

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References

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[2] Tokyo Metropolitan Government. Latest updates on COVID-19 in Tokyo. https://stopcovid19.metro.tokyo.lg.jp/. [Accessed 30 June 2020].

[3] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.

[4] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. J Am Med Assoc 2020:e206775. https://doi.org/10.1001/jama.2020.6775.

[5] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region—case series. N Engl J Med 2020;382:2012–22. https://doi.org/10.1056/NEJMoa2004500.

[6] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81. https://doi.org/10.1016/S2213-2600(20)30079-5.

[7] Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.4326.

[8] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020. https://doi.org/10.1001/jama.2020.5394.

[9] Nakamura K, Hikone M, Shimizu H, Kuwahara Y, Tanabe M, Kobayashi M, et al. A sporadic COVID-19 pneumonia treated with extracorporeal membrane oxygenation in Tokyo, Japan: a case report. J Infect Chemother 2020;26:756–61. https://doi.org/10.1016/j.jiac.2020.03.018.

[10] Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38:1573–82. https://doi.org/10.1007/s00134-012-2682-1.

[11] Shimazu H, Yoshiya K, Maruyama S, Kanayama S, Matsunami S, Iwamura H, et al. The efficacy of combination therapies including antiviral drugs, methylprednisolone and daily proning in 20 patients with COVID-19 requiring invasive mechanical ventilation- case series in a single critical care center in Osaka, Japan. Arch Clin Med Case Rep 2020;4:867–82.

[12] Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160:389–97. https://doi.org/10.7326/M13-2486.

[13] Duggal A, Pinto R, Rubenfeld G, Fowler RA. Global variability in reported mortality for critical illness during the 2009–10 influenza A(H1N1) pandemic: a systematic review and meta-regression to guide reporting of outcomes during disease outbreaks. PloS One 2016;11:e0155044. https://doi.org/10.1371/journal.pone.0155044.

[14] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 preliminary report. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2007764. NEJMoa2007764.

[15] Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa1176. ciaa1176.

[16] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19 preliminary report. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2021436. NEJMoa2021436.

[17] Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68. https://doi.org/10.1056/NEJMoa1214103.

[18] Pan C, Chen L, Lu C, Zhang W, Xia JA, Sklar MC, et al. Lung recruitability in COVID-19-associated acute respiratory distress syndrome: a single-center observational study. Am J Respir Crit Care Med 2020;201:1294–7. https://doi.org/10.1164/rccm.202003-0527LE.