


# Clinical Characteristics and Treatments Modalities of Patients with COVID-19 Infection During the Early Phase of the Epidemic: A Single-Center from Turkey

Deniz Borcak<sup>1</sup>, Musa Balta<sup>2</sup>, Erkan Bulut<sup>3</sup>, Şerife Ozalp<sup>4</sup>, Yusuf Çelik<sup>5</sup>, Tuncay Güler<sup>6</sup>, Mehmet Akif Güllü<sup>1</sup>, Mehmet Dokur<sup>7</sup>

<sup>1</sup>Department of Infectious Diseases and Clinical Microbiology, Beylikdüzü State Hospital, İstanbul, Turkey

<sup>2</sup>Department of Emergency Medicine, Beylikdüzü State Hospital, İstanbul, Turkey

<sup>3</sup>Department of Ophthalmology, Beylikdüzü State Hospital, İstanbul, Turkey

<sup>4</sup>Department of Anesthesiology and Critical Care, Beylikdüzü State Hospital, İstanbul, Turkey

<sup>5</sup>Department of Biostatistics, Biruni University, Faculty of Medicine, İstanbul, Turkey

<sup>6</sup>Department of Chest Disease, Beylikdüzü State Hospital, İstanbul, Turkey

<sup>7</sup>Department of Emergency Medicine, Biruni University Faculty of Medicine İstanbul, Turkey

## ABSTRACT

**Objective:** The emergence of coronavirus disease 2019 is a major healthcare threat. We aimed to assist in the management of coronavirus disease 2019 infection and contribute to the literature so the hospitals may find the information about our strategies useful in their efforts to reduce the challenges they are facing in this retrospective single-center study.

**Methods:** We analyzed the data of 1260 laboratory or radiologically confirmed hospitalized cases with coronavirus disease 2019 infection to determine the clinical and epidemiological characteristics. An infectious and a chest disease physician followed all the cases and recorded demographic data, clinical signs, treatment, laboratory, and radiological findings.

**Results:** The mean age of the patients was 51.96 years old, and 665 (52.7%) were male. The most commonly experienced symptoms at the onset of illness were cough, shortness of breath, myalgia, and fever. Most patients showed normal leucocytes counts, lymphopenia, elevated levels of C-reactive protein, procalcitonin, ferritin, lactate dehydrogenase, and creatine kinase.

**Conclusion:** Recognizing the changing treatment modalities is especially important for the management of the coronavirus disease 2019 pandemic.

**Keywords:** clinical, COVID-19 pandemic, medicine, modalities, therapeutics

## INTRODUCTION

Severe acute respiratory syndrome (SARS) coronavirus disease-2019 (COVID-19) is the causative agent of coronavirus disease 2019, which was declared a global pandemic by the World Health Organization on March 11, 2020.<sup>1,2</sup> The coronavirus belongs to a family of viruses that can cause various symptoms, including fever, difficulty breathing, and pulmonary infections. These viruses are widespread in animals, but relatively few cases have been known to affect humans.<sup>3,4</sup> From March 11, 2020, the number of infected people increased and COVID-19 spread rapidly throughout Turkey. The science committee of the Turkish Ministry of Health developed guidance on novel coronavirus for healthcare professionals. Algorithms and obligations regarding how to manage the disease were included in the guidance.<sup>5,6</sup>

Guidelines for the treatment of this infection may vary from country to country. In general, it is characterized by atypical pneumonia and is usually confirmed by a positive RNA test or computed tomography (CT) of the lung.<sup>7</sup> Different diagnostic techniques, such as serological, molecular, and radiological, can assist health centers in the detection of COVID-19; among others, the radiological method is the most recommended and is able to diagnose the infection quickly and accurately with fewer false-negatives. It is very important to use effective methods for the diagnosis of infections, which is essential for saving patients' lives and preventing the transmission of infection to other people.<sup>8,9</sup>

The majority of the cases show mild symptoms. Rapid progression may occur at the early stage of the disease.<sup>10</sup> To improve the

**Cite this article as:** Borcak D, Balta M, Bulut E, et al. Clinical characteristics and treatments modalities of patients with COVID-19 infection during the early phase of the epidemic: A single-center from Turkey. *Eur J Ther.* 2022;28(2):135-141.

**Corresponding author:** Deniz Borcak, e-mail: drdenizborcak@gmail.com

**Received:** May 11, 2021 **Accepted:** November 24, 2021



Copyright@Author(s) – Available online at eurjther.com.

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

prognosis of the disease, early control of viral replication and implementation of host-directed therapy are necessary. As a new infectious disease, it is particularly important to find out its clinical characteristics, mainly in the early stage, which is helping to detect and isolate patients earlier and to minimize its spread.

This retrospective research was conducted during the first 2 months of the current COVID-19 outbreak at a 360-bed state hospital in İstanbul, Turkey the epicenter of the outbreak was in İstanbul, Turkey. In order to manage patient flow and hospital capacity, we provided outpatient care in our hospital for patients with less severe symptoms. All non-urgent elective surgeries, endoscopies, or other invasive procedures were canceled through the peak period to reduce the risk transmission to patients and to provide adequate hospital capacity. We established screening and triage protocols for suspected cases in the emergency unit.

Since the onset of the outbreak, many agents that could have efficacy against COVID-19 have been suggested. The clinical experience of countries will lead to the use of drugs with proven efficacy and safety in the management of the infection. We aimed to report the initial experience with clinical features and the management of patients with COVID-19 infection in Turkey.

## METHODS

Hospitalized patients 18 years of age and older due to possible infection of COVID-19 in compliance with the Turkish, Turkey Ministry of Health's General Directorate of Public Health's COVID-19 guide from March 11, 2020, when the first case was reported in Turkish, Turkey until May 11, 2020, were reported in this study. All cases were followed by an infectious and chest disease physician, and demographic data, clinical signs, treatment, laboratory, and radiological findings were recorded at presentation, during the hospital stay, and before discharge. Cases were confirmed either by CT or reverse transcriptase-polymerase chain reaction tests [RT-PCR] performed on nasopharyngeal and oropharyngeal swab specimens. In the very early stages of infection, when the nasopharyngeal swab may still be negative, CT plays a significant role in ultimately diagnosing COVID-19 in highly suspicious patients. Therefore, low-dose CT scanning was performed for the patients before hospitalization. Experienced chest radiologists analyzed all images as compliant or not compliant with COVID-19 pneumonia.<sup>11</sup>

### Main Points

- Management of coronavirus disease 2019 pandemic has changed considerably from the beginning until now.
- Hydroxychloroquine has been replaced by specific antiviral agents.
- C-reactive protein, ferritin, D-dimer, lactate dehydrogenase, elevated liver function, and leukopenia are significant initial laboratory findings for clinical progress.
- Age group of pandemic victims is higher at the onset of the pandemic.
- Mask, social distance, and isolation are always important in protection from contamination.

At the onset of the epidemic, patients received hydroxychloroquine [HCQ] as initial therapy, according to Turkish COVID-19 guidelines. Hydroxychloroquine 400 mg was given twice daily for 1 day, followed by 200 mg twice daily for 4 more days. Hydroxychloroquine was usually combined with ceftriaxone (2 g once daily) plus azithromycin (500 mg on D1 followed by 250 mg per day for the next 4 days). Electrocardiograms (ECG) were performed on each patient before treatment and 2 days after initiation of treatment. When the QTc was >500 ms, the treatment was either not initiated or discontinued. Furthermore, during treatment, any drug potentially prolonging the QT interval was discontinued. Favipiravir therapy was started in patients with severe disease who did not respond to HCQ. Symptomatic therapies, including oxygen, were added when needed. Antibiotic treatment was modified in patients who were clinically unresponsive to the initial therapy. When needed, standard blood chemistry was checked. Until then, inpatients already receiving treatment with improved clinical outcomes and effective adherence to treatment were discharged due to a critical need to admit new, untreated inpatients. Patient follow-up continued in outpatient policlinics as much as possible.

## Statistical Analysis

It was planned to use multivariate statistical methods instead of univariate statistical methods to increase the internal validity and accuracy of the analysis in the evaluation of the COVID-19 data. Mean and standard deviation [SD] were calculated for continuous variables. The normality of the variables was analyzed using a Kolmogorov–Smirnov test. The Student's *t*-test was used to compare the means between the 2 groups. A chi-square test was used to analyze the differences of drugs in the treatment of COVID-19 and to analyze the frequency of patients who survived or did not survive. The receiver operator characteristic [ROC] curve analysis was used to calculate the diagnostic accuracy as defined by the area under the curve [AUC], being 95% CI. Two-sided *P*-values were considered statistically significant at  $P \leq .05$ . All statistical analyses were carried out by using R software/programming [version 3.6.2 [2019-12-12] – CRAN].

## Ethical Statement

All authors declare that the research was conducted in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects." Data collection and analysis of all subjects were approved by the ethics committee of Biruni University (Date: May 28, 2020, Decision no: 2020/40-04).

## RESULTS

From March 11 to May 11, 2020, a total of 1260 patients confirmed with either CT findings or RT-PCR tests for COVID-19 were hospitalized. Among all patients, 776 (61.6%) tested positive for COVID-19 RT-PCR on nasopharyngeal and oropharyngeal swab tests. The mean [ $\pm$ SD] age of the patients was  $51.96 \pm 15.63$  years (range: 19\_104). Overall, 52.7% (665 of 1260 patients) were male.

Hypertension was the most common comorbidity, affecting 190 (15.1%) of patients with available data. The second most

common comorbidities were diabetes (131 patients, 10.4%) and chronic obstructive pulmonary disease (86 patients, 6.8%). Only 74 patients (5.9%) had a history of cardiovascular disease. Clinical characteristics ranged from an asymptomatic carrier to acute respiratory distress syndrome and multiorgan failure on a large scale. The demographic and clinical characteristics of the patients are shown in Table 1.

The most common clinical symptoms in these patients were cough and shortness of breath, followed by myalgia and fever consistent with the literature.

We monitored major laboratory markers from the onset of illness. In survivors, the baseline lymphocyte count was higher than in non-survivors. Levels of C-reactive protein, D-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, creatine kinase, and procalcitonin were clearly elevated in non-survivors compared with survivors throughout the clinical course and increased with disease worsening. Table 2 shows the laboratory findings of the patients on admission.

Oseltamivir was given in 94.6% of all cases. Convalescent plasma therapy was administered to 30.4% of non-survivors, and no transfusion reactions occurred.

The majority (1203, 95.48%) of patients had a favorable outcome and were discharged from our unit. Fifty-seven patients were transferred to the intensive care unit (ICU), of whom 16 improved

and were then returned to the ward. Almost 64.91% of non-survivors required invasive mechanical ventilation. We found the mortality rate for COVID-19 cases as 4.52% (Table 3).

### DISCUSSION

The most frequently used agents both in Turkey and all over the world for the treatment of COVID19 are HCQ, lopinavir/ritonavir, favipiravir, and remdesivir. Antiviral drugs administered shortly after symptom onset can reduce infectiousness to others by reducing viral shedding in the respiratory secretions of patients. Hydroxychloroquine has already been prescribed to many people for the treatment or prophylaxis of malaria and some rheumatological disorders. Notably, the drug shows antiviral activity in vitro against coronaviruses and specifically, COVID-19.<sup>12</sup> Clinical trials from China and France revealed potential benefits using HCQ, sometimes combined with the macrolide-type antibiotic azithromycin resulting in a more rapid reduction in viral shedding and improved clinical outcomes.<sup>13,14</sup> We performed an ECG before the treatment because of reports about heart complications with this drug in patients with underlying conditions. Patients at risk were hospitalized for ECG monitoring allowing for the early detection and treatment of possible cardiac side effects. The toxicity of HCQ did not pose a major problem in our study. Also, favipiravir is an RNA-dependent RNA polymerase inhibitor and has been shown to be effective in the treatment of influenza and the Ebola virus.<sup>15,16</sup> Favipiravir was given orally. The dose was 1600

**Table 1.** Demographics and Clinical Characteristics

Characteristics	Non-survivor (n=57) (%)	Survivor (n=1203) (%)	All cases (n=1260) (%)	P
Age (mean)	65.74 ± 12.86	51.31 ± 15.45	51.96 ± 15.63	.000
Female/male	24.6/75.4	48.3/51.7	47.2/52.7	.000
Hypertension	21.7	14.8	15.1	.363
Cardiovascular disease	21.7	5	5.9	.001
Chronic obstructive lung disease	8.7	6.7	6.8	.706
Diabetes	30.4	9.3	10.4	.001
Malignancy	4.3	0.7	0.9	.073
Fever	65.2	61.4	61.6	.716
Cough	78.3	82.4	82.2	.615
Sputum production	73.9	64.5	65	.358
Dyspnea	91.3	69.8	70.9	.027
Chest pain	56.5	17.4	19.4	.000
Palpitation	47.8	10	12	.000
Nausea	30.4	57.9	56.4	.010
Diarrhea	17.4	15.2	15.3	.780
Headache	21.7	31.7	31.2	.317

**Table 2.** Laboratory Findings of Patients Infected with COVID-19 on Admission to Hospital

	Non-survivor n = 57 (min-max)	Survivor n = 1203 (min-max)	All cases n = 1260 (min-max)	P
White cell count, $\times 10^9/L$	12.918 (0.85–49.01)	6.85213 (1.29–30.84)	7.13 (0.85–49.01)	.000
Neutrophil count, $\times 10^9/L$	11.124 (0.63–40.64)	4.506 (0.05–26.78)	4.81 (0.05–40.64)	.000
Lymphocyte count, $\times 10^9/L$	1.195 (0.1–4.9)	1.721 (0.3–13.3)	1.69 (0.1–13.3)	.000
Hemoglobin, g/L	11.561 (7–16.1)	13.492 (4.8–19.5)	13.4 (4.8–19.5)	.009
Platelet count, $\times 10^9/L$	226.772 (75–1167)	254.164 (52–685)	226.4 (52–1167)	.985
D-dimer, mg/L	6.310 (0.3–35.2)	1.602 (0.19–15.1)	2.03 (0.19–35.2)	.008
Glucose	195.228 (90–523)	128.151 (62–487)	131.58 (62–523)	.000
Urea	94.185 (25–392)	31.391 (7.7–236)	34.4 (7.7–392)	.000
Creatine, $\mu\text{mol/L}$	1 (0.5–8.4)	1.110 (0.3–8)	0.99 (0.3–8.4)	.606
Aspartate aminotransferase, U/L	74.109 (17–1071)	32.678 (4–929)	34.71 (4–1071)	.040
Alanine aminotransferase, U/L	47.339 (18–472)	31.299 (16–321)	32.11 (16–472)	.093
Sodium, mmol/L	142.536 (127–171)	138.355 (115–152)	138.56 (115–171)	.001
Potassium mmol/L	4.00 (2.6–6.2)	4.27 (2.8–5.9)	3.8 (2.6–6.2)	.217
Creatine kinase U/L	594.806 (29–4585)	166.936 (17–4108)	189.27 (17–4585)	.001
Lactate dehydrogenase, U/L	526.727 (190–1333)	281.301 (77–949)	293.57 (77–1333)	.000
C-reactive protein, mg/L	132.785 (1.24–396)	43.555 (0.1–371)	47.73 (0.1–396)	.000
Procalcitonin ng/ml	4.722 (0.3–9.25)	1.805 (0.12–6.1)	3.42 (0.12–9.25)	.197
Ferritin	996.506 (263–2000)	365.452 (9.6–2000)	392.85 (9.6–2000)	.000

**Table 3.** Treatments and Outcomes of Patients Infected with COVID-19

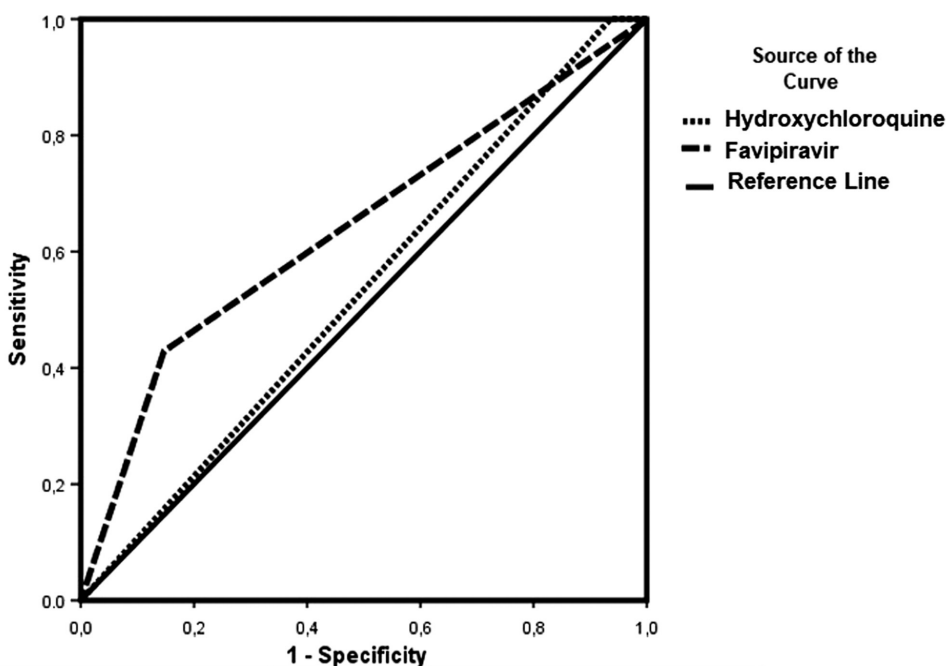
Pharmacological Treatments	Non-survivor (n = 57) %	Survivor (n = 1203) %	All cases (n = 1260) %	P
Hydroxychloroquine	95.7	96.9	96.8	.738
Oseltamivir	91.3	94.8	94.6	.476
Favipiravir	52.2	7.4	9.7	.000
Azithromycin	69.6	88.3	87.4	.008
Clarithromycin	8.7	16	15.6	.350
Levofloxacin	13	29	28.2	.097
Moxifloxacin	8.7	4.8	5	.398
Ceftriaxone	91.3	96.7	96.4	.180
Piperacillin-tazobactam	39.1	15.2	16.5	.003
Meropenem	26.1	2.6	3.8	.000
Prednisolone	30.4	3.1	4.5	.000
Immune plasma	30.4	0.2	1.8	.000

mg twice daily on day 1 and 600 mg twice daily on days 2-5. If we look at the mortality rates, we can see variations between reports. For example, Guan et al<sup>17</sup> report a death rate of 1.4% while Baud et al<sup>18</sup> report 5.7%. China has resulted in very remarkable results as the patients receiving favipiravir showed cleared viral load in 4 days as compared to 11 days in patients receiving standard care only.<sup>19,20</sup> Favipiravir is in vitro active against COVID-19, and early clinical experience is encouraging in the management of the ongoing pandemic coronavirus. We found the mortality rate for COVID-19 cases to be 4.52%. When we compared mortality rates in our study, the patient group receiving favipiravir was found to be lower than the group receiving HCQ. It has been shown that favipiravir has a protective effect on death (Figure 1). The course of the disease is more modifiable at an early stage, so treatment needs to be started before patients become critically ill. It is understood that antiviral treatment is more likely to have benefits for both influenza and SARS when it is started early during the course of the disease.<sup>16</sup> The outcomes of several randomized controlled trials to test the efficacy of favipiravir for COVID-19 will further identify the role of this drug. Patients infected with COVID-19 are being treated empirically with oseltamivir, but there is little evidence

from randomized controlled trials to support the treatment of coronavirus infections with oseltamivir. Oseltamivir, an Food and Drug Admission-approved drug for influenza A and B treatment, inhibits the viral neuraminidase and ultimately prevents the release of viral particles from host cells.<sup>21</sup> In order to detect influenza viruses in respiratory specimens, no diagnostic tests were available, so oseltamivir was administered in 85% of all cases for possible influenza infection in our study.

We also examined the impact of advanced age on mortality rates in our research. A well-known fact now is the rise in mortality with old age for COVID-19. Advanced age has been reported as an independent predictor of death for SARS and the Middle East respiratory syndrome. Early Chinese reports showed that the mortality rate could be 3 times higher in older patients especially those at age over 80.<sup>22</sup> Lvliang Lu et al<sup>23</sup> confirmed that advanced age is associated with mortality in their systematic review. An Italian study reported that COVID-19 has had the greatest impact on those aged over 50, by ICU mortality being 26%, whereas it was 36% for those aged over 65.<sup>24</sup> In our study, we found that the majority of those who did not survive from coronavirus were male patients, older patients, and patients with comorbidities,

Figure 1. Receiver operating characteristic (ROC) curve prediction for favipiravir and hydroxychloroquine in mortality of the patients.



Area Under the Curve					
variables	Area	SE	P	95%CI	
				Lower Bound	Upper Bound
Favipiravir	0.641	0.070	0.033	0.504	0.778
Hydroxychloroquine	0.532	0.063	0.627	0.409	0.655

ROC Curve



indicating that these patients may have an elevated risk of serious disease or death.

At the time of hospital admission, we analyzed the laboratory data of patients and made a comparison between the patients who died and those who survived in our study. However, in connection, increasingly higher inflammatory markers (C-reactive protein, ferritin, D dimer, lactate dehydrogenase, elevated liver function, and leukopenia) are significant initial laboratory findings in patients who have not survived as in other studies.<sup>25-28</sup> Liver injury in patients with coronavirus infections is often transient and can be directly caused by the viral infection of liver cells.<sup>29</sup> Changes in the number of different blood cells, including leukocytes, lymphocytes, neutrophils, platelets, and hemoglobin, may show the form and severity of the disease.<sup>30</sup>

### Limitations

Our study has some notable limitations. Firstly, it was conducted during the global pandemic's early months and the condition was uncertain. It was based upon the limited data available to us as of May 11, 2020. Some cases had incomplete documentation of the exposure history and laboratory testing. This is a single-centered, retrospective analysis and it may be restricted to the critical care resources of the hospital and may not be valid in all other regions. Secondly, some specific clinical data, such as time to the disease onset, was missing. Further research is still required.

### CONCLUSION

The clinical features and treatment processes related to COVID-19 pandemic have changed from the beginning until now. Since the beginning of the pandemic isolation, quarantine, social distance and social protection programs have been our choices due to the lack of adequate vaccines and effective treatment. We hope that our patient population will have a better understanding and baseline characteristics, hospital course, and clinical results will give useful information to physicians who are working in a time of exceptional volume and uncertainty.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Biruni University (Date: May 28, 2020, Decision no: 2020/40-04).

**Informed Consent:** Since our study was a retrospective data study, informed consent was not required.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – D.B., M.B.; Design – D.B., M.B.; Supervision – E.B., M.D.; Funding – T.G., M.A.G.; Materials – D.B., M.B.; Data Collection and/or Processing – D.B., Ş.Ö.; Analysis and/or Interpretation – Y.Ç., E.B.; Literature Review – X.X., X.X.; Writing – D.M., E.B.; Critical Review – D.B., M.D.

**Acknowledgements:** The authors thank to all medical staff who worked hard during the COVID 19 pandemic.

**Declaration of Interests:** The authors declare that they have no conflict of interest.

**Funding:** The authors declared that this study has received no financial support.

### REFERENCES

1. Provenzani A, Polidori P. Covid-19 and drug therapy, what we learned. *Int J Clin Pharm.* 2020;42(3):833-836. [\[CrossRef\]](#)
2. Trapani D, Marra A, Curigliano G. The experience on coronavirus disease 2019 and cancer from an oncology hub institution in Milan, Lombardy Region. *Eur J Cancer.* 2020;132:199-206. [\[CrossRef\]](#)
3. Adhikari SP, Meng S, Wu YJ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Pover.* 2020;9(1):29. [\[CrossRef\]](#)
4. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect.* 2020;80(4):388-393. [\[CrossRef\]](#)
5. Infection guideline for COVID19/SARS COV2 (Turkish ministry of Health-2020). Available at: [https://COVID19bilgi.saglik.gov.tr/depo/rehberler/COVID-19\\_Rehberi.pdf](https://COVID19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf). Accessed 03.01.2021.
6. Kilic AU, Kara F, Alp E, Doganay M. New threat: 2019 novel coronavirus infection and infection control perspective in Turkey. *North Clin Istanb.* 2020;7(2):95-98. [\[CrossRef\]](#)
7. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382(8):727-733. [\[CrossRef\]](#)
8. Ozma MA, Maroufi P, Khodadadi E, et al. Clinical manifestation, diagnosis, prevention and control of COVID-19 (COVID-19) during the outbreak period. *Infez Med.* 2020;28(2):153-165.
9. Long C, Xu H, Shen Q, et al. Diagnosis of the coronavirus disease (COVID-19): rRT-PCR or CT? *Eur J Radiol.* 2020;126:108961. [\[CrossRef\]](#)
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506. [\[CrossRef\]](#)
11. Carotti M, Salaffi F, Sarzi-Puttini P, et al. Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists. *Radiol Med.* 2020;125(7):636-646. [\[CrossRef\]](#)
12. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (COVID-19). *Clin Infect Dis.* 2020;71(15):732-739. [\[CrossRef\]](#)
13. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-271. [\[CrossRef\]](#)
14. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* 2020;56(1):105949. [\[CrossRef\]](#)
15. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral Res.* 2013;100(2):446-454. [\[CrossRef\]](#)
16. Şimşek Yavuz S, Ünal S. Antiviral treatment of COVID-19. *Turk J Med Sci.* 2020;50(SI-1):611-619. [\[CrossRef\]](#)
17. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720. [\[CrossRef\]](#)
18. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. *Lancet Infect Dis.* 2020;20(7):773. [\[CrossRef\]](#)
19. Ahsan W, Javed S, Bratty MA, Alhazmi HA, Najmi A. Treatment of COVID-19: how far have we reached? *Drug Discov Ther.* 2020;14(2):67-72. [\[CrossRef\]](#)
20. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering (Beijing).* 2020;6(10):1192-1198. [\[CrossRef\]](#)

21. Naveed M, Uddin S, Abdullah KS, Ishaq SE, Ahmad T. Various evidence-based hypothetical and experimental treatment approaches and their effectiveness against COVID-19 worldwide: a comprehensive literature review. *EJMO*. 2020;4:265-285. [\[CrossRef\]](#)
22. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242. [\[CrossRef\]](#)
23. Lu L, Zhong W, Bian Z, et al. A comparison of mortality-related risk factors of COVID-19, SARS, and MERS: a systematic review and meta-analysis. *J Infect*. 2020;81(4):e18-e25. [\[CrossRef\]](#)
24. Grasselli G, Zangrillo A, Zanella A, et al. COVID-19 Lombardy ICU network. Baseline characteristics and outcomes of 1591 patients infected With COVID-19 admitted to ICUs of the Lombardy region, Italy. *JAMA*. 2020;323(16):1574-1581. [\[CrossRef\]](#)
25. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ*. 2020;369:m1996. [\[CrossRef\]](#)
26. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. [\[CrossRef\]](#)
27. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol*. 2020;92(7):797-806. [\[CrossRef\]](#)
28. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the seattle region - case series. *N Engl J Med*. 2020;382(21):2012-2022. [\[CrossRef\]](#)
29. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*. 2020;5(5):428-430. [\[CrossRef\]](#)
30. Okabayashi T, Kariwa H, Yokota S, et al. Cytokine regulation in SARS coronavirus infection compared to other respiratory virus infections. *J Med Virol*. 2006;78(4):417-424. [\[CrossRef\]](#)