

# Results of Favipiravir Combined Treatment in Intensive Care Patients With Covid-19

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## Research

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# Abstract

**Aim:** Covid-19 (Coronavirus disease 2019) is a disease that has already taken place in human history. Although there is still no effective treatment and vaccine protocol, different treatment options are being tried. In this study, it was aimed to determine the basic characteristics and changes in laboratory findings of patients who were hospitalized with the diagnosis of Covid-19 in the intensive care unit and underwent treatment protocol containing favipiravir.

**Material and Method:** It was carried out with the data of 179 inpatients in an intensive care unit between 01.06.2020 - 30.06.2020. The inclusion criterias of the study are to have a diagnosis of COVID-19 confirmed by PCR test, to be hospitalized in the intensive care unit, receiving therapy combined with favipiravir and to have access to its data through the automation system. According to literature; the sociodemographic characteristics, some basic characteristics and some laboratory findings of the patients were evaluated. Statistical analyzes were performed using the Statistical Package for Social Sciences (SPSS) version 24.0 (IBM Corp .; Armonk, NY, USA).

**Findings:** The average age of the study group is  $60.9 \pm 16.4$  years and 65.9% (n:118) of them are male. According to the clinical classification, more than half (50.8%, n: 91) are included in the "high" clinical classification. The most common chronic disease is "hypertension (HT)" (42.5%, n:76) and the most common symptom is "fever" (57.5%, n: 103). While 82.7% (n: 148) have widespread CT (Computed tomography) findings, CPR (C-Reactive protein) positivity rate is 65.4% (n: 117). Statistical significant difference was detected between three measurements of blood urea nitrogen (BUN), aspartat aminotransferase (AST), alanin aminotransfrase (ALT), CRP between the 1st and the 3rd day.

**Conclusion:** Favipiravir demonstrates a proper safety profile. However, its side effects teratogenicity, hyperuricaemia and QTc (corrected QT interval) prolongation have not yet been adequately studied. It may be safe and tolerable in short-term use, but more evidence is needed to assess the longer-term effects of treatment.

## Introduction

In the twentieth century, three new life-threatening diseases caused by coronavirus emerged. These are middle east respiratory syndrome (MERS), severe acute respiratory syndrome (SARS) and the new lung disease Covid-19 (1). All of them belong to the Coronaviridae family; kind of viruses that possess a positive-sense single-stranded RNA genome. Similar to other RNA viruses, this family is characterized by significant genetic variability and high recombination rate that enable them distributed easily among humans and animals worldwide (2). Covid-19 appeared in Wuhan, China in December 2019; it is a disease caused by the 2019 novel Coronavirus (2019-nCoV) that manifests itself with viral pneumonia in most patients (3). Due to its high infectivity and fatality rate; moreover, the absence of specific medicine for 2019-nCoV, outbreak of the disease has brought heavy burden to the world.

Symptoms in Covid-19; may range from mild illness to acute respiratory distress syndrome. The common characteristics of people with severe disease are; showing lymphocytopenia, being old and smoking (4). In addition, in a meta-analysis consisting of 15 studies, it was stated that severe disease was associated with an underlying hypertension, diabetes, and a respiratory or cardiac pathology (5).

So far, there is no treatment protocol and vaccination for Covid-19 with proven safety and efficacy. Today, the main treatments are shaped according to our experiences with similar viruses such as SARS-Cov and MERS-Cov (3). In addition to symptomatic treatments; different treatment methods such as remdesivir, chloroquine and hydroxychloroquine, kaletra, favipiravir, tocilizumab, and stem cell therapy are used (6, 7). As the virus causes endothelial dysfunction, procoagulant conditions and renin-angiotensin-aldosterone system imbalance; use of low molecular weight heparin, low dose aspirin, angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) in the early period is also recommended (8). Despite all this; there is currently no effective treatment available for coronavirus infections. Hard works have been made to develop vaccines and therapeutic drugs. Preclinical evidence has proven the potential of several countermeasures, yet large scale trials are still needed (2).

Favipiravir, one of the mentioned treatment methods; is a kind of RNA-dependent RNA polymerase (RdRp) inhibitor, blocking RNA virus replication. It is a potential antiviral agent used against SARS-CoV-2 (9). Favipiravir is active against a variety of influenza viruses including A (H1N1) pdm09, A (H5N1) and A (H7N9) avian influenza viruses, and has a synergistic effect with oseltamivir (10). It is an approved treatment for influenza. Besides; less studies has been published for favipiravir to treat SARS-CoV-2 compared to remdesivir. Indeed, favipiravir was approved by the National Medical Products Administration of China as the first anti-COVID-19 drug in March 2020, as the clinical trial had demonstrated efficacy with minimal side effects (2). It accelerates clinical recovery by reducing respiratory problems (3). The effective dose of favipiravir used is 1600 mg twice daily (first day), 600 mg twice daily (days 2–5) and it not used more than 14 days. However, favipiravir is contraindicated in pregnant women because of teratogenicity and embryotoxicity in animals (10, 11). Since the effectiveness and tolerability of hydroxychloroquine in treatment contain some question marks; recently, researchers have started to work mostly on remdesivir and favipiravir (8). In contrast to remdesivir, the studies on favipiravir in vitro and in vivo is limited. However, there are still three active clinical trials regarding favipiravir that have begun enrolling patients in China (12).

The Covid-19 pandemic stands as a serious health threat to humanity. The data obtained show that; the treatment approaches applied especially for patients who are being treated during the intensive care period, can make serious differences on prognosis. In this study, it was aimed to determine the basic characteristics and changes in laboratory findings of patients who were hospitalized with the diagnosis of Covid-19 in the intensive care unit of a training and research hospital and underwent treatment protocol containing favipiravir.

## Material And Method

The study was planned in a prospective, cross-sectional way. It was carried out with the data of inpatients at the Health Sciences University Istanbul Bağcılar Training and Research Hospital Adult Intensive Care Unit between 01.06.2020–30.06.2020. The inclusion criterias of the study are to have a diagnosis of COVID-19 confirmed by PCR test, to be hospitalized in the intensive care unit, receiving favipravir combined therapy and to have access to its data through the automation system. The study includes data from 179 patients who meet these criteria.

According to literature; the sociodemographic characteristics, some basic characteristics and some laboratory findings of the patients were obtained from the hospital computer records.

Statistical analyzes were performed using the Statistical Package for Social Sciences version 24.0 (IBM Corp .; Armonk, NY, USA). Mean and standard deviation are given for the variables obtained by measurement, number and percentage distributions for the data obtained by counting. Friedman test in non-parametric conditions and ANOVA (Repeated Measure) test for repeated measurements in parametric conditions were used in comparison of admission, 1st day and 3rd day values of laboratory examination results. Statistical significance level was accepted as  $p < 0.05$  considering the 95% confidence interval and 5% margin of error.

Shapiro-Wilk test was used to adapt to normal distribution in the evaluation of parametric conditions. It was observed that BUN and procalcitonin 3rd day values did not comply with the normal distribution ( $p < 0.05$ ). Therefore, the Friedman test, which is a non-parametric test, was used in the analysis of these values. The ANOVA (Repeated Measure) test was used for repeated measurements, as the others conformed to the normal distribution. While evaluating the test results, Wilks'Lambda p value was taken into consideration when  $p < 0.05$  according to Mauchly Sphericity test.

## **Findings:**

One hundred seventy nine patients were included in the study. The average age of the study group is  $60.9 \pm 16.4$  years and 65.9% (n:118) of them are male. According to the clinical classification, more than half (50.8%, n: 91) are included in the "high" clinical classification. The most common chronic disease is "hypertension (HT)" (42.5%, n:76) and the most common symptom is "fever" (57.5%, n: 103). While 82.7% (n: 148) have widespread CT findings, PCR positivity rate is 65.4% (n: 117). The main characteristics of the patients are summarized in the table below (Table 1).

Laboratory measurements were carried out in intensive care hospitalization, on the 1st day and on the 3rd day. Some laboratory results, which were reported to have changed in the literature, were taken into consideration. Statistical significant difference was detected between three measurements of blood urea nitrogen (BUN), aspartat aminotransferase (AST), alanin aminotransfrase (ALT), C-reactive protein (CRP). In the pairwise comparisons, it was found that the hospitalization values were lower than the others. There was no significant difference between three measurements in terms of other values (Table 2).

## Discussion

In Japan, favipiravir was approved as a stockpile against influenza pandemics and was distributed as an option against for SARS-CoV-2 under government control. Still, the efficacies of antiviral therapies have not been clarified clearly in the course of these patients. However, in the literature, there is a case report that emphasize recovery two days after favipiravir treatment. This case suggest that favipiravir may be contributed to the amelioration of the lung lesion in Covid-19 (13).

In a large scale study, among the 1,023 deaths, the majority were among patients of  $\geq 60$  years of age. The  $\geq 80$  age group was characterized by the highest fatality rate (20.3%) among all age groups (14). Relatively fewer cases were reported among young children (0–9 years-old). While more males were affected by the disease, the male-to-female ratio varies between different populations. As the pathogen has been extraordinarily contagious, no deaths have occurred in mild or even severe cases; but the fatality rate reached 49% among patients that were classified as critical cases (14). These findings are compatible with the presented study.

In a prospective, multicenter, open-label, randomized superiority trial examined the efficacy of favipiravir versus arbidol for treating COVID-19 (15). There was no difference in the 7-day clinical recovery rate for favipiravir versus arbidol in the overall population. However, this difference existed for a subgroup of non-critical patients without hypertension or diabetes (15). Three registered clinical trials are planned regarding the use of favipiravir against COVID-19 (16, 17, 18). The presented study was performed in an intensive care unit and parallel to the mentioned studies; 42.5% of the patients (n:76) had hypertension and 29.1% (n:52) had diabetes mellitus.

In the presented study, the most common symptom was "fever" (57.5%, n:103) and second symptom was dispnea (42.5%, n:76). In a similar study; major symptom at the onset of illness was again fever (88.7%) (5). The other symptoms were cough (67.8%), fatigue (38.1%), dyspnea (18.7%), and myalgia (14.9%). Additionally; these symptoms could be followed by sputum production, dizziness, headache, vomiting, abdominal pain, diarrhea, sore throat, nasal congestion and rhinorrhoea (5). Differently; in a small study two patients reported diarrhea, one had liver injury and one had poor diet (19). The recent study from China reported favipiravir had fewer side effects such as diarrhea and transaminitis in non-transplant COVID-19 (20).

There are some studies about the heart related disorders during medical treatment combined with favipiravir. A study that reports prolonged QT interval due to favipiravir has been encountered (19). In another study; two patients who were followed-up in the Intensive Care Unit (ICU) with favipiravir combined treatment developed ventricular tachycardia; both had increased T peak to T end (Tp-e) interval and Tp-e/QTc ratio despite normal QTc intervals before treatment (21). In the presented study 23.5% (n:42) of the patients had heart disease during the hospitalization but no heart related problem was detected during follow-up.

In the presented study; no significant adverse reactions were noted related with favipiravir combined treatment group. In another study, favipiravir had significantly fewer adverse effects than the lopinavir/ritonavir group (22). Similarly; in the trial conducted on patients with COVID-19 indicated better results in patients treated with favipiravir than the group treated with lopinavir/ritonavir. Additionally, less side effects were noted in the treatment group (20).

Studies have reported that lymphocytopenia occurs in severe types of Covid-19 (23). Again; lymphocytopenia and hyponatremia were detected in a patient who recovered after treatment for Covid-19 pneumonia (24). In a Japanese clinical trial with 501 patients, the main adverse reactions were detected as rising uric acid (n:24, 4.79%), diarrhea (n:24, 4.79%), neutropenia (n:9, 1.80%), increased AST (n:9, 1.80%) and increased ALT (n:8, 1.60%) (25). In a trial of favipiravir with patients with COVID-19, the most common adverse events were liver enzyme abnormalities, psychiatric, gastrointestinal symptoms and serum uric acid elevations (26). The overall adverse reactions were mild symptoms, but pregnant woman should not be treated with favipiravir (25). In the presented study, serum uric acid levels were not evaluated but liver enzyme abnormalities were detected parallel to the literature.

## Conclusion

Favipiravir demonstrates a proper safety profile. However, its side effects teratogenicity, hyperuricaemia and QTc prolongation have not yet been adequately studied. It may be safe and tolerable in short-term use, but more evidence is needed to assess the longer-term effects of treatment.

## Abbreviations

ACEI: Angiotensin Converting Enzyme Inhibitor

ALT: Alanin aminotransferase

ARB: Angiotensin 2 Receptor Blocker

AST: Aspartat aminotransferase

BUN: Blood urea nitrogen

Covid-19: Coronavirus Disease 2019)

CRP: C-Reactive protein

CT: Computed tomography

HT: Hypertension

ICU: Intensive care unit

MERS: Middle East Respiratory Syndrome

PCR: Polymerase Chain Reaction

QTc: Corrected QT interval

RdRp: RNA-dependent RNA polymerase

SARS: Severe Acute Respiratory Syndrome

SPSS: Statistical Package for Social Sciences

Tp-e: T Peak to T end

2019-nCoV: 2019-novel Coronavirus

## Declarations

### **\*Ethics approval and consent to participate**

It was approved by the Ethics Committee of Istanbul Göztepe Training and Research Hospital with the decision number 2020/0243. In addition; TR Ministry of Health Scientific Research Platform on Covid-19 has also obtained a work permit with the date 05.09.2020 and number T175416.

### **\*Consent to publication**

Not applicable

### **\*Availability of data and material**

Not applicable

### **\*Competing interests:**

There is no financial or non-financial conflict of interest

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### **\*Authors' contributions**

Habip Yilmaz: Drafting the work, substantial contributions to the conception of the work, acquisition, analyses, final approval of the version to be published

Emre Guner: Collected the data, final approval of the version to be published

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## References

1. Tsitoura E, Bibaki E, Bolaki M, Vasarmidi E, Trachalaki A, Symvoulakis EK, et al. Treatment strategies to fight the new coronavirus SARS-CoV: A challenge for a Rubik's Cube solver. *Exp Ther Med* 2020;20(1):147-50.
2. Tu YF, Chien CS, Yarmishyn AA, Lin YY, Luo YH, Lin YT, et al. A review of SARS-CoV-2 and the ongoing clinical trials. *Int J Mol Sci* 2020;21(7):2657.
3. Yousefi B, Valizadeh S, Ghaffari H, Vahedi A, Karbalaei M, Eslami M. A global treatments for coronaviruses including COVID-19. *J Cell Physiol* 2020 May 11; DOI: 1002/jcp.29785
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-20.
5. Matsushita K, Ding N, Kou M, et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: a systematic review and meta-analysis. *medRxiv* 2020. DOI:10.1101/2020.04.05.20054155
6. INSERM: Launch of a European clinical trial against COVID-19 (press release). Accessed March 22, 2020.
7. World Health Organization: Launch of SOLIDARITY trial (press release). Accessed March 18, 2020.
8. Rempert A, Gerlei Z, Creprekal O, Wagner L, Foldes K, Marton A, et al. Guidance on the special care of liver or kidney transplant recipients diagnosed with Covid-19. *Orv Hetil* 2020;161(32):1310-21.
9. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19) *Drug Discov Ther* 2020;14:58–60.
10. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antiviral Research* 2018;153:85–94.
11. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacology & Therapeutics* 2020;209:107512.
12. Duan Y. Advance of promising targets and agents against COVID-19 in China. *Drug Discov Today* 2020;25(5):810-2.
13. Takahashi N, Abe R, Hattori N, Taniguchi T, Igari H, Nakada T. Clinical course of a critically ill patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *J Artif Organs* 2020;16:1-4.
14. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020;395:507-13.

15. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020 doi: 2020.03.17.20037432.
16. gov. Various combination of protease inhibitors oseltamivir favipiravir hydroxychloroquine for treatment of COVID-19: a randomized control trial (THDMS-COVID-19). <https://clinicaltrials.gov/ct2/show/NCT04303299>, 2020.
17. gov. Favipiravir combined with tocilizumab in the treatment of corona virus disease. <https://clinicaltrials.gov/ct2/show/NCT04310228>, 2020.
18. Newswire PR: Sihuan pharmaceutical announces clinical research of favipiravir, co-developed with the Academy of Military Medical Sciences of the People's Liberation Army, has commenced. Sihuan Pharmaceutical Holdings Group Ltd, 2020. <https://en.pnasia.com/releases/apac/sihuan-pharmaceutical-announces-clinical-research-of-favipiravir-co-developed-with-the-academy-of-military-medical-sciences-of-the-people-s-liberation-army-has-commenced-273880.shtml>.
19. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing). Epub ahead of print 18 March 2020. DOI: 10.1016/j.eng.2020.03.007.
20. Chinello P, Petrosillo N, Pittalis S, et al. QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient San Francisco, CA, USA: Public Library of Science, 2017.
21. Yenerçağ M, Arslan U, Doğduş M, Günal Ö, Öztürk ÇE, Aksan G, et al. Evaluation of electrocardiographic ventricular repolarization variables in patients with newly diagnosed COVID-19. J Electrocardiol 2020;62:5–9.
22. <http://www.szdsyy.com/News/0a6c1e58-e3d0-4cd1-867a-d5524bc59cd6.html> (accessed February 22, 2020). (in Chinese).
23. Antonio R, Silvia M. Immunosuppression drug-related and clinical manifestation of coronavirus disease 2019: A therapeutical hypothesis. Am J Transplant. 2020. 10.1111/ajt.15905
24. Guillen E, Pineiro GJ, Revuelta I, et al. Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation? Am J Transplant. 2020:1-4. 10.1111/ajt.15874
25. A Pharmacokinetics study of favipiravir in patients with severe influenza <https://clinicaltrials.gov/ct2/show/NCT03394209>.
26. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020 DOI: 10.1101/2020.03.17.20037432.

## Tables

**Table 1.** Basic characteristics of the patients

<b>Group with favipiravir in the treatment regimen (n:179)</b>	
<b>Gender n (%)</b>	
Female	61 (34.1)
Male	118 (65.9)
<b>Age n (%)</b>	
<65	107 (59.8)
≥65	72 (40.2)
<b>Clinical classification n (%)</b>	
Mild	1 (0.6)
Moderate	87 (48.6)
High	91 (50.8)
<b>Hypertension n (%)</b>	76 (42.5)
<b>Diabetes mellitus n (%)</b>	52 (29.1)
<b>Chronic obst. pul. disease n (%)</b>	15 (8.4)
<b>Asthma n (%)</b>	9 (5.0)
<b>Hearth disease n (%)</b>	42 (23.5)
<b>Cancer n (%)</b>	5 (2.8)
<b>Symptoms n (%)</b>	
Fever	103 (57.5)
Dispnea	76 (42.5)
Runny nose	4 (2.2)
<b>Pneumonia n (%)</b>	175 (97.8)
<b>Tomography findings n (%)</b>	
Local	22 (12.3)
Common	148 (82.7)
No evidence	9 (5.1)
<b>PCR positivity n (%)</b>	117 (65.4)

**Table.2** Changes in some of the laboratory measurements

Laboratory findings	Average (hospitalization) (SS)		Average (1st day) (SS)		Average (3rd day) (SS)		F	p
Leukocyte	7.73	(4.06)	8.12	(4.20)	8.26	(4.50)	2.072	0.129 <sup>b</sup>
Lymphocyte	1.28	(0.89)	1.17	(0.81)	1.23	(0.68)	1.758	0.175 <sup>b</sup>
BUN	42.96	(28.77)	42.07	(33.24)	42.71	(36.87)	19.94 <sup>a</sup>	<b>0.000<sup>a</sup></b>
Creatine	1.33	(1.13)	1.34	(1.31)	1.28	(1.07)	0.409	0.665 <sup>b</sup>
AST	47.51	(151.69)	57.97	(255.23)	63.54	(168.25)	3.186	0.044 <sup>b</sup>
ALT	38.51	(47.49)	43.40	(63.79)	69.41	(171.97)	5.075	<b>0.044<sup>b</sup></b>
CRP	83.83	(74.60)	116.22	(77.69)	89.80	(79.50)	23.538	<b>0.007<sup>b</sup></b>
Procalcitonin	1.28	(3.14)	116.22	(77.69)	89.80	(79.50)	0.199 <sup>a</sup>	<b>0.007<sup>b</sup></b>
Ferrite	1049.48	(3642.24)	2.26	(9.18)	2.87	(11.44)	2.474	<b>0.000<sup>b</sup></b>
D-dimer	1304.16	(2611.16)	1227.24	(3574.78)	1177.04	(3108.06)	3.557	0.905 <sup>a</sup>
Fi	45.70	(28.62)	2081.61	(4273.28)	2201.09	(3693.58)	0.498	0.090 <sup>b</sup>
PaO <sub>2</sub>	70.43	(27.65)	53.85	(25.91)	54.80	(26.83)	1.980	<b>0.031<sup>b</sup></b>
			68.24	(30.24)	82.72	(24.90)		0.617 <sup>b</sup>
								0.219 <sup>b</sup>

<sup>a</sup> Friedman test, chi-square and p

<sup>b</sup> On repetitive scale, ANOVA test, Wilks'Lambda