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Does Favipiravir Reduce Mortality in Patients with COVID-19 ARDS and Severe Pneumonia?

COVID-19 ARDS ve Ağır COVID Pnömonisi Hastalarında Favipiravir Mortaliteyi Azaltır Mı?

Received/Geliş Tarihi : 11.05.2021
Accepted/Kabul Tarihi : 08.12.2021

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Turkish Journal of Intensive Care published by Galenos
Publishing House.

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ABSTRACT Objective: Although there is no antiviral treatment specific to the virus, favipiravir has entered the treatment routine as an antiviral in our country in May 2020. In this study, in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) acute respiratory distress syndrome (ARDS) in the intensive care unit; The effects of favipiravir antiviral regimen on mortality and morbidity were evaluated.

Materials and Methods: Patients admitted to the intensive care unit were divided into two groups as those who received favipiravir (group F; n=208) and those who did not (group N; n=101). The treatment of the cases is arranged according to current national guidelines. Metavision/QlinICU Clinical Decision Support Software, in intensive care unit; Acute Physiology and Chronic Health Evaluation-II, Sequential Organ Failure Assessment score, aspartate aminotransferase, alanine aminotransferase, urea, creatinine, lactate dehydrogenase, ferritin, C-reactive protein (CRP), procalcitonin, Pro-BNP, D-dimer, fibrinogen, white blood cell, neutrophil count (NEU), lymphocyte count (LYM), NEU/LYM, CRP, t1 acceptance (0th hour), t2 follow-up (24th hour) and t3 (discharge or ex) values of acute phase parameters, and the comorbidity is obtained by Structured Query Language queries. The primary outcome is mortality; secondary outcomes are possible drug-related organ toxicities, sudden change of the level of the acute phase reactants, requirement of continuous renal replacement therapy (CRRT), hospitalization time, ventilator dependent days.

Results: One hundred eight women (35%), 201 men (65%), a total of 309 cases were evaluated in the study. In the demographic data of the groups, no statistically significant difference was found between the frequency of comorbidity, mortality rate, CRRT need, and secondary infection. The mean increase of 107.66±628.99 units between the t1 and t3 measurement was found to be statistically significant in F group cases. In the F group, the neutrophil/lymphocyte ratio (NLR) during the follow-up period and the last NLR were found to be lower than the initial value.

Conclusion: It was determined that favipiravir used in the treatment of SARS-CoV-2 ARDS has no superiority in preventing mortality.

Keywords: Favipiravir, COVID-19, ARDS, mortality

ÖZ Amaç: Virüse özgü antiviral tedavi olmamakla birlikte, favipiravir Mayıs 2020'de ülkemizde antiviral olarak tedavi rutinine girmiştir. Bu çalışmada yoğun bakım ünitesinde şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) akut solunum sıkıntısı sendromlu (ARDS) hastalarda favipiravir antiviral rejiminin mortalite ve morbidite üzerindeki etkileri değerlendirildi.

Gereç ve Yöntem: Yoğun bakım ünitesine kabul edilen hastalar, favipiravir alanlar (grup F; n=208) ve almayanlar (grup N; n=101) olarak iki gruba ayrıldı. Olguların tedavisi güncel ulusal kılavuzlara göre düzenlendi. Metavision/QlinICU Yoğun Bakım Ünitesi'nde Klinik Karar Destek Yazılımı; Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II, komorbidite, Sıralı Organ Yetmezliği Değerlendirmesi skoru, aspartat aminotransferaz, alanin aminotransferaz, üre, kreatinin, laktat dehidrogenaz, ferritin, C-reaktif protein (CRP), prokalsitonin, Pro-BNP, D-dimer, fibrinojen, beyaz kan hücresi, nötrofil sayısı (NEU), lenfosit sayısı (LYM), NEU/LYM, CRP, t1 kabulü (0. saat), akut faz parametrelerinin t2 takip (24. saat) ve t3 (taburcu veya eks) değerleri, Yapısal Sorgulama Dili (Structured Query Language) sorguları ile elde edilir. Birincil sonuç mortalitedir; ikincil sonuçlar, ilaca bağlı olası organ toksisiteleri, akut faz reaktanlarının seviyesinde ani değişiklik, sürekli renal replasman tedavisi (CRRT) gereksinimi, hastanede kalış süresi, ventilatöre bağlı günlerdir.

Bulgular: Çalışmada 108 kadın (%35), 201 erkek (%65), toplam 309 olgu değerlendirildi. Grupların demografik verilerinde komorbidite sıklığı, mortalite oranı, CRRT ihtiyacı ve sekonder enfeksiyon arasında istatistiksel olarak anlamlı fark bulunmadı. F grubu olgularda t1 ve t3 ölçümleri arasında 107,66±628,99 birimlik ortalama artış istatistiksel olarak anlamlı bulundu. F grubunda takip süresince nötrofil/lenfosit oranı (NLO) ve son NLO başlangıç değerinden düşük bulundu.

Sonuç: SARS-CoV-2 ARDS tedavisinde kullanılan favipiravirin mortaliteyi önlemede üstünlüğü olmadığı belirlendi.

Anahtar Kelimeler: Favipiravir, COVID-19, ARDS, mortalite

Introduction

Currently, there isn't any precise effective antiviral treatment specific to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that causes coronavirus disease-2019 (COVID-19) disease (1). Since there is no known specific antiviral treatment, generic antiviral agents such as remdesivir, hydroxychloroquine and chloroquine, favipiravir, lopinavir-ritonavir (lop/r), umifenovir, and ribavirin are used in the management of the disease (2). In our country, Hydroxychloroquine and/or favipiravir are still recommended in the Treatment Guide for Adult Patients with COVID-19 created by the Scientific Committee (latest update 29/06/2021) (3) and these drugs are routinely used in all patients.

Favipiravir is a new type of drug that is a RNA dependent RNA polymerase inhibitor. Therefore, favipiravir may have potential antiviral effect on SARS-CoV-2, an RNA virus (4). In a clinical study conducted in China which favipiravir and lop/r were compared shows that favipiravir has stronger antiviral activity (5).

Several scoring methods such as Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Health Assessment-II (APACHE-II) score are used in intensive care units (ICU) for mortality prediction; some biomarkers are also used for this purpose. Factors such as advanced age (≥ 65 years of age), accompanying comorbidities, high fever (> 39 °C), lymphopenia, neutrophilia, C-reactive protein (CRP) level, serum ferritin level, coagulation parameters (D-dimer and prothrombin time) have been shown to increase the risk of severe pneumonia and developing of acute respiratory distress syndrome (ARDS) (6).

The COVID-19 pandemic is a health problem that affects the whole world and the antiviral treatments used in the treatment of the disease are still being updated. As in our country, favipiravir is recommended in treatment guidelines in many countries and it is routinely used for many patients. In this study, we aimed to reveal the effects of favipiravir as an antiviral regimen used in the treatment of patients with severe pneumonia and ARDS associated with COVID-19 on mortality and morbidity in the ICU.

Materials and Methods

After the approval of the Turkish Ministry of Health Clinical Research Board; our study was approved by the Local Ethics Committee of the Bakırköy Dr. Sadi Konuk

Training and Research Hospital with the decision number 2020/389 (date: 07.09.2020).

The treatment of patients with severe pneumonia and ARDS associated with COVID-19 admitted to Health Sciences University Turkey Bakırköy Dr Sadi Konuk Training and Research Hospital Anesthesiology and Reanimation Department ICU are reviewed observationally and retrospectively between 15 March 2020 and 29 November 2020 in this study. We examined 208 patients who had favipiravir in their treatment regimen (named as group F) (2x1,600 mg at first day as a loading dose, followed by 2x600 mg per day in next 4-9 days, 5-10 days treatment in total) and 101 patients who had not favipiravir in their treatment regimen (named as group N).

According to the current guideline (7); the patients infected by SARS-CoV-2 were diagnosed with polymerase chain reaction (PCR) test in the first line. The diagnosis was determined in PCR negative patients through positive chest computed tomography scan or/with lower respiratory tract infection findings such as fever, cough, dyspnea.

Severe pneumonia was described according to the Surviving Sepsis Campaign Guidelines on the Management of Adults with COVID-19 (7), and ARDS was described according to the Berlin criteria (8).

The study was planned as a retrospective observational study on the systemic effects of antiviral treatment before and after updates in the Treatment Guide for Adult Patients with COVID-19 compiled by the Ministry of Health's General Directorate of Public Health. Standardized supportive treatments were applied to both groups of patients; such as antibiotic therapy directed to the source in the presence of secondary infection, sedation agents, nutritional support, cardiovascular support therapy, steroids, immunomodulatory drugs, non-invasive positive pressure ventilation or invasive ventilation therapy, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation treatment for patients whom conventional mechanical ventilation support is insufficient for. Since both groups were followed by the same intensive care team and with the same treatment protocol, we think that there is no obvious difference in terms of supportive treatments.

Cases with procalcitonin level > 1 during follow-up were considered to be accompanied by secondary infection.

Patients younger than 18 years old, patients were followed for less than 24 hours in ICU, patients were pregnant or breastfeeding, patients whose treatment

was interrupted due to drug side effects were excluded from the study. We determined the primary outcome as mortality and secondary outcomes as possible drug-related organ toxicities, sudden change of the level of the acute phase reactants, requirement of CRRT, hospitalization time, ventilator dependent days.

Demographic data of patients diagnosed with COVID-19 pneumonia or ARDS in the Anesthesiology and reanimation intensive care unit registered in 'ImdSoft-Metavision/QlinICU Clinical Decision Support Software'. APACHE-II, SOFA score, level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, lactate dehydrogenase (LDH), ferritin, CRP, procalcitonin, Pro-BNP, D-dimer, fibrinogen, white blood cell (WBC), neutrophil count (NEU), lymphocyte count (LYM), NEU/LYM ratio, acute phase parameters at admission (0th hour), at follow-up (24th hour) and at discharge or time of death is obtained by Structured Query Language queries. Admission time is defined as t1, 24th hour of follow up defined as t2, and discharge or exitus time defined as t3. The presence of secondary infection was decided through procalcitonin level >1 during follow-up.

Statistical Analysis

The Number Cruncher Statistical System program was used for statistical analysis. Descriptive statistical methods (to identify the mean, standard deviation, median, frequency, percentage, minimum value, maximum value) were used for evaluating the study data. The suitability of quantitative data to normal distribution was tested by Shapiro-Wilk test and graphical analysis. Student t-test was used for comparing parametric quantitative variables between two groups. T-test and Mann-Whitney U test were used to compare non-parametric quantitative variables to analyze quantitative independent data. Paired samples test was used for in-group comparisons of quantitative variables with normal distribution. The Wilcoxon signed-rank test was used for in-group comparisons of non parametric quantitative variables and for analysis of dependent quantitative data. Pearson chi-square test and Fisher-Freeman-Halton Exact test were used to analyze and compare qualitative independent data. The distribution of variables is measured by the Kolmogorov-Smirnov test. The SPSS 27.0 program was used in the analyzes. Statistical significance was accepted as $p < 0.05$.

Results

Of the patients participating in the study, 35% (n=108) were female and 65% (n=201) were male. The ages of the cases ranged from 18 to 100, and the mean value was 60.29 ± 16.56 years. There was no statistically significant difference in terms of age, height, weight and gender distributions between the two groups. Total mortality rate was 48.5%, and there was no statistically significant difference between the mortality rates between group F (48.6%) and group N (48.5%). There was no statistically significant difference between the groups in terms of secondary outcomes, comorbidities, the presence of secondary infection and horowitz index at the time of admission to intensive care unit (t1). There was no statistically significant difference in APACHE-II and SOFA scores between the groups at t1. The ratio of the intubated patients was similar in both groups ($p < 0.05$) (Table 1).

The increases in AST level between t1 and t2, by an average of 99.23 ± 1294.29 units and between t1 and t3, by an average of 446.75 ± 1868.19 units were found to be statistically significant ($p = 0.014$; $p = 0.005$). The difference between AST level between at t1 and t2 in F group cases was found to be statistically significantly higher than the group N cases ($p = 0.039$).

The mean increase of ALT level from t1 to t3 is 107.66 ± 628.99 units, it was found to be statistically significant in F group cases ($p = 0.001$). The transaminase levels of the groups are shown in Table 2.

The urea and creatinine levels of the cases do not show statistically significant differences depending on the groups ($p > 0.05$).

Acute phase physiological parameters such as CRP, ferritin, LDH, D-dimer, procalcitonin, and fibrinogen levels were evaluated. There was no difference between the groups in the follow-up process. Hemogram parameters were evaluated, no significant difference was observed in WBC levels at t1, t2 and t3 times in group F and group N cases. No significant difference was observed in the lymphocyte levels between group F and group N. A significant increase was found in the lymphocyte levels at t3 of both groups compared to the initial measurement (t1) ($p < 0.05$). In the F group, the neutrophil/lymphocyte ratio (NLR) during the follow-up period and the last NLR were found to be lower than the initial value ($p < 0.05$) (Table 3).

Discussion

Favipiravir was reported to be particularly useful in the treatment of mild to moderate disease with its safety and efficacy profile (9,10). Unlike these studies, our patients were critically ill patients and we didn't determine any difference in mortality.

Clinical trials of COVID-19 infection in China suggest that favipiravir has a faster viral clearance than lop/r and better recovery rate than umifenovir and has a positive effect on morbidity and mortality (10,11). Favipiravir + INF inhalation and lop/r + INF inhalation treatment was compared in a

total of 80 COVID-19 patients in a study conducted by Chen et al. (11). It was shown that the favipiravir group has shorter viral clearance time (4 days, 11 days) and better radiological recovery rate (91.4%, 62.2%) compared to the other group in this study. The frequency of side effects was also found to be less in the favipiravir group. Contrary to these literature, no reduction in mortality was observed in patients receiving favipiravir in our study.

In a randomized clinical study in China comparing favipiravir and umifenovir as antiviral therapy, recovery rates on the seventh day of the treatment were examined, no significant difference was found between these two

Table 1. Comparisons of descriptive characteristics between groups

		Groups			p
		Total	Favipiravir	Non-favipiravir	
Age (year)	Min-max (median)	18-100 (62)	18-100 (61.5)	19-87 (62)	^a 0.809
	Mean ± SD	60.29±16.56	60.45±17.17	59.96±15.32	
Gender n (%)	Female	108 (35.0)	78 (37.5)	30 (29.7)	^b 0.178
	Male	201 (65.0)	130 (62.5)	71 (70.3)	
Height (m)	Min-max (median)	1.4-1.96 (1.7)	1.4-1.96 (1.7)	1.4-1.87 (1.7)	^a 0.333
	Mean ± SD	1.69±0.09	1.68±0.09	1.69±0.09	
Weight (kg)	Min-max (median)	35-180 (80)	35-180 (80)	50-165 (80)	^a 0.554
	Mean ± SD	78.99±17.8	78.57±18.41	79.85±16.52	
BMI (kg/m ²)	Min-max (median)	14.69-55.6 (26.3)	14.69-55.6 (26.2)	19.53-53.88 (26.3)	^a 0.770
	Mean ± SD	27.71±5.93	27.64±6.02	27.85±5.78	
Length of stay (hours)	Min-max (median)	1-1348 (146)	1-1348 (147)	1-744 (146)	^c 0.976
	Mean ± SD	216.03±215.01	220.12±226.25	206.68±187.65	
Duration of mechanical ventilation (hours)	Mean ± SD	188.29±189.44	191.23±200.40	182.14±165.08	^c 0.866
Mechanical ventilation type	Invasive	239 (77.3)	163 (78.4)	76 (75.2)	^b 0.539
	HFNC	70 (22.7)	45 (21.6)	25 (24.8)	
Horowitz index (t1)	Mean ± SD	209.79±114.69	210.54±113.72	208.16±117.46	^a 0.879
SOFA (t1)	Min-max (median)	-	0-23 (9)	0-44 (9)	^a 0.243
	Mean ± SD	-	8.55±5.13	9.35±5.93	
APACHE-II (t1)	Min-max (median)	-	2-44 (21)	4-42 (21)	^a 0.560
	Mean ± SD	-	20.88±8.93	21.55±9.17	
Duration of CRRT (hours)	Mean ± SD	103.81±122.27	95.78±106.39	122.21±153.68	^c 0.915
Mortality (%)	Survival	159 (51.5)	107 (51.4)	52 (51.2)	^d 1.000
	Non-survival	150 (48.5)	101(48.6)	49 (48.5)	
Comorbidity (%)	No	113 (36.6)	72 (4.6)	41 (40.6)	^b 0.306
	Yes	196 (63.4)	136 (65.4)	60 (59.4)	
Secondary infection (%)	No	140 (45.3)	93 (44.7)	47 (46.5)	^b 0.763
	Yes	169 (54.7)	115 (55.3)	54 (53.5)	

^aStudent t test, ^bPearson chi-square test, ^cMann-Whitney U test, ^dFisher Exact test, HFNC: high-flow nasal cannula, min: minimum, max: maximum, SD: standard deviation, BMI: body mass index, APACHE-II: Acute Physiology and Health Assessment-II, CRRT: continuous renal replacement therapy, SOFA: Sequential Organ Failure Assessment

drugs (11). Ribavirin + corticosteroid as a standard treatment in newly diagnosed SARS-CoV-1 patients and lop/r + ribavirin + corticosteroid treatment was compared by Chan et al. (10). at the time of the SARS-CoV-1 epidemic. A statistically significant difference was found in terms of mortality and ARDS development on the 21st day in this study.

In a randomized controlled trial including 199 COVID-19 cases, patients received standard care (SC) + lop/r or only SC were compared. It was stated that lop/r + SC was not different from SC in terms of time of clinical recovery and mortality in 28 days. (lop/r + SC 19.2%, SC 25%). The authors stated that lop/r does not contribute to SC in the treatment of patients infected by COVID-19. They stated that although mortality was reported as 11-14.5% in patients hospitalized

due to COVID-19, the high rate of mortality 22.1% in this study might be due to the fact that the patients included in the study were severe patients (12).

Our study was conducted in patients followed-up in intensive care. Total mortality is 48.5%, and there is no significant difference between the groups.

Favipiravir has a well-characterized safety profile over 4,000 patients. Similar rates of side effects have been reported between low and high doses of favipiravir. Gastrointestinal side effects, increased uric acid levels, decreased neutrophil count, increased AST and ALT levels, psychiatric symptom reactions, and increased blood lipid profile are among the common side effects. The rates of serious side effects are 0.4% and 1.1% (13). Use of favipiravir in patients with moderate renal impairment

Table 2. Evaluation of AST and ALT Levels between groups

		Groups		p
		Favipiravir	Non-favipiravir	
AST level (t1) (U/L)	Min-max (median)	9-5884 (49.5)	12-6,106 (60)	°0.047*
	Mean ± SD	164.82±574.03	200.12±668.64	
AST level (t2) (U/L)	Min-max (median)	8-15,026 (40)	12-9,282 (40)	°0.338
	Mean ± SD	264.05±1333,67	192.49±946.93	
AST level (t3) (U/L)	Min-max (median)	8-15,026 (59)	12-12,688 (55)	°0.467
	Mean ± SD	613.53±1868,65	625.27±1837,29	
Difference between AST level (t1-t2) (U/L)	Difference	99.23±1294,29	-7.63±1160,16	°0.039*
	p	°0.014*	°0.001**	-
Difference between AST level (t1-t3) (U/L)	Difference	446.75±1868,19	424.63±1649,89	°0.533
	p	°0.005**	°0.162	-
ALT level (t1) (U/L)	Min-max (median)	3-7,174 (29)	2-4,772 (53)	°0.003**
	Mean ± SD	116.91±538.64	171.61±541.43	
ALT level (t2) (U/L)	Min-max (median)	4-8,184 (28)	2-9,124 (36)	°0.068
	Mean ± SD	129.88±638.41	242.83±1074,17	
ALT level (t3) (U/L)	Min-max (median)	4-4,076 (37)	2-9124 (50)	°0.067
	Mean ± SD	224.57±592.22	387±1174,11	
Difference between ALT level (t1-t2) (U/L)	Difference	12.97±370.05	71.22±1204,85	°0.090
	p	°0.217	°0.022*	-
Difference between ALT level (t1-t3) (U/L)	Difference	107.66±628.99	226.26±1014,91	°0.641
	p	°0.001**	°0.091	-

°Mann-Whitney U test, °Wilcoxon signed-ranks test, *p<0.05, **p<0.01, min: minimum, max: maximum, SD: standard deviation, ALT: alanine aminotransferase, AST: aspartate aminotransferase

[Glomerul filtration rate (GFR) between 30-60 mL/min] results in a 1.5-fold increase in C_{trough} compared to patients with normal renal function. However, there is no evidence for its use among patients with GFR <30 mL/min (14).

Organ toxicities that affect mortality were examined in our study, an increase was observed in AST and ALT levels in the favipiravir group, however this did not cause toxic hepatitis in the cases. There was no significant difference in the times of the CRRT need, urea and creatinine levels

Table 3. Evaluation of NEU, LYM levels and NEU/LYM ratio between groups

		Groups		p
		Favipiravir	Non-favipiravir	
t1 NEU levels (x10 ³) (μL)	Min-max (median)	0.01-36.99 (9.97)	1.92-56.11 (10.55)	°0.188
	Mean ± SD	11.07±6.52	12.65±8.06	
t2 NEU levels (x10 ³) (μL)	Min-max (median)	0.32-56.11 (9.24)	1.44-56.11 (10.09)	°0.055
	Mean ± SD	10.56±6.82	12.33±8.03	
t3 NEU levels (x10 ³) (μL)	Min-max (median)	0.01-45.91 (9.22)	0.92-51.96 (9.29)	°0.789
	Mean ± SD	11.05±8	12.79±11.31	
Difference between NEU levels t1-t2(x10 ³) (μL)	Difference	-0.51±5.88	-0.32±5.52	°0.701
	p	^f 0.074	^f 0.407	
Difference between NEU levels t1-t3 (x10 ³) (μL)	Difference	0.09±8.19	0.33±10.41	°0.495
	p	^f 0.585	^f 0.454	
t1 LYM levels (x10 ³) (μL)	Min-max (median)	0.07-5.86 (0.67)	0.18-7.33 (0.8)	°0.133
	Mean ± SD	0.88±0.68	1.05±0.96	
t2 LYM levels (x10 ³) (μL)	Min-max (median)	0.04-4.08 (0.8)	0.07-5.86 (0.87)	°0.487
	Mean ± SD	0.97±0.66	1.1±0.89	
t3 LYM levels (x10 ³) (μL)	Min-max (median)	0.07-4.2 (1.03)	0-6.25 (1.09)	°0.226
	Mean ± SD	1.23±0.83	1.42±1.1	
Difference between LYM levels t1-t2 (x10 ³) (μL)	Difference	0.09±0.72	0.05±1.04	°0.796
	p	^f 0.004**	^f 0.038*	
Difference between LYM levels t1-t3 (x10 ³) (μL)	Difference	0.36±0.83	0.39±0.93	°0.793
	p	^f 0.001**	^f 0.001**	
t1 NEU/LYM ratio	Min-max (median)	0.08-177.29 (13.16)	2.96-113.96 (12.17)	°0.798
	Mean ± SD	17.2±16.54	17.51±16.24	
t2 NEU/LYM ratio	Min-max (median)	0.48-181 (11.39)	1.64-251.29 (11.52)	°0.704
	Mean ± SD	15.5±17.71	19.23±28.88	
t3 NEU/LYM ratio	Min-max (median)	0.08-81.11 (8.65)	0.51-125.63 (7.98)	°0.534
	Mean ± SD	12.43±12.09	14.12±19.28	
Difference between NEU/LYM ratio t1-t2	Difference	-1.70±18.84	1.71±25.03	°0.415
	p	^f 0.002**	^f 0.299	
Difference between NEU/LYM ratio t1-t3	Difference	-4.81±18.77	-3.51±21.02	°0.943
	p	^f 0.001**	^f 0.001**	

[°]Mann-Whitney U test, ^fWilcoxon signed-ranks test, *p<0.05, **p<0.01, min: minimum, max: maximum, SD: standard deviation, NEU: neutrophil count, LYM: lymphocyte count

during follow-up between the groups. It was demonstrated that the cases included in our study had a similar clinical status in terms of known organ failure at the beginning of the intensive care unit.

In COVID-19 patients, coagulopathy with high D-dimer level and high fibrinogen level are frequently encountered. The group with high D-dimer values was found to be associated with higher mortality in a study (15). Increased D-dimer levels and normal fibrinogen levels were shown as laboratory evidence of COVID-19 disease in a study by Mucha et al. (14). In our study, no relationship was shown between D-dimer levels and mortality rates between these groups. Fibrinogen value was generally found to be normal or high.

Henry et al. (16) found that ferritin levels of deceased patients were higher than normal in a study they conducted. Likewise, in another study conducted in China, it was stated that it may be beneficial to monitor ferritin values in high-risk patients (17). In our study, ferritin values in both groups at the time of admission were also found to be higher than normal values. In our study, there was no significant difference in the follow-up of both groups in terms of acute phase reactants.

Deng et al. (18) compared non survival and survival patients in their study, they concluded that increased leukocyte count and decreased lymphocyte count were associated with mortality. Since there was no significant change in the presence of secondary infection between the groups, it suggests that the increased leukocyte count is not directly related to secondary infection. It has been determined that the cytokine release syndrome is associated with decreased lymphocyte level in new types of coronavirus patients (19). Significant reduction of T lymphocytes has been associated with mortality and is considered a poor prognosis factor and has been associated with disease severity in severely ill patients (20). When lymphocyte levels were evaluated in our study, the lymphocyte levels of the both groups were low at the time of hospitalization, a significant improvement was found in both groups during and at the end of the treatment. In a multicenter retrospective cohort study that included 60 inpatients and 42 outpatients, a total of 102 patients, NLR was calculated from hemogram parameters. As a result, advanced age, high LDH and high NLR values were considered as poor prognostic parameters in COVID-19 patients and hospitalization was recommended to such patients (21). In our study, in the F group, the NLR was found

to be lower than the initial value during the follow-up period and during discharge, however we could not find any effect of this situation on mortality.

It is difficult to conduct controlled studies in such a life-threatening epidemic. Therefore, the study was planned as a retrospective observational study. It was unethical to allocate patients to receive different experimental drugs, and a randomization process was impossible. Therefore, we chose to conduct a before-after-designed study in which patients hospitalized in two consecutive periods were included in two groups, respectively. Lack of randomization, the absence of standard control groups and the additional use of glucocorticoids and lop/r made it difficult to evaluate the effect of favipiravir. The limitations of our study are that; it is retrospective and viral clearance was not examined.

Conclusion

There are many factors affecting mortality and morbidity in COVID-19 patients followed up in intensive care. In our study, no significant difference was found in terms of mortality and secondary outcome related favipiravir treatment in intensive care units. We determine that favipiravir treatment causes significant increases in liver enzymes. Therefore, we think that liver enzyme levels should be monitored more tightly in favipiravir treatment.

Ethics

Ethics Committee Approval: After the approval of the Turkish Ministry of Health Clinical Research Board; our study was approved by the Local Ethics Committee of the Bakırköy Dr. Sadi Konuk Training and Research Hospital with the decision number 2020/389 (date: 07.09.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Z.L.A., S.A., Concept: K.Z.L.A., R.Y., S.A., Y.T.Ş., Design: R.Y., Y.T.Ş., Data Collection or Processing: K.Z.L.A., E.G., S.A., Analysis or Interpretation: E.G., S.A., Y.T.Ş., Literature Search: K.Z.L.A., R.Y., Writing: R.Y., Y.T.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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