ORIGINAL ARTICLE

The effects of favipiravir on hematological parameters of covid-19 patients

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http://dx.doi.org/10.1590/1806-9282.66.S2.65

SUMMARY

INTRODUCTION: *This study aims to evaluate changes in hematological parameters after the follow-up of patients who received treatment with favipiravir due to COVID-19 infections.*

METHODS: *Sixty-two cases receiving favipiravir treatment for at least five days due to COVID-19 infection were evaluated retrospectively. Parameters including age, gender, nasopharyngeal swab positivity, and chronic diseases were analyzed. Hematologic parameters were analyzed before and after the treatment.*

RESULTS: *The mean age of the patients receiving treatment with favipiravir was 63.7±12.3 years. Nasopharyngeal swab positivity was detected in 67.7%. The most common comorbid conditions detected in patients were hypertension in 25 cases (40.3%) and diabetes in 16 cases (25.8%). In the statistical analysis of the hematological parameters before and after treatment with favipiravir, WBC, PT-PTT-INR levels were found to be unaffected; the mean RBC was found to have decreased from 4.33 ± 0.58 M/uL to 4.16 ± 0.54 M/uL (p:0.003); the median hemoglobin level was found to have decreased from 12.3 g/dl to 11.9 g/dl (p:0.041); the hematocrit level decreased from 38.1% ± 4.8 to 36.9% ± 4.2 (p:0.026); the median neutrophil count decreased from 4.57 K/uL to 3.85 K/uL (p:0.001); the mean lymphocyte count increased from 1.22 ± 0.53 K/uL to 1.84 ± 1.19 K/uL (p:0.000); and the mean platelet count increased from 244.1 ± 85.1 K/uL to 281.9 ± 103.3 K/uL (p:0.005).*

CONCLUSION: *We concluded that the pathological effect of treatment with favipiravir on the hematologic system was the suppression in the erythrocyte series, and there were no adverse effects in other hematologic parameters.*

KEYWORDS: *Coronavirus Infections. Antiviral Agents. Blood. Blood Cells. Favipiravir.*

DATE OF SUBMISSION: 03-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
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INTRODUCTION

Sars-Corona Virus 2, (COVID-19) is a coronavirus that first appeared in China in December 2019, causing severe acute respiratory failure[1,2]. It has infected more than five million people as of May 2020. Worldwide, hydroxychloroquine, favipiravir, lopinavir, remidesivir, tocilizumab, and anakinra are the main drugs used for the treatment of COVID-19. Favipiravir is an antiviral drug developed against many RNA viruses (influenza, West Nile, yellow fever, flaviviruses, arenaviruses, bunyaviruses, and alphaviruses), acting by inhibiting RNA-dependent RNA polymerase[3,4]. Yet, in 2020, China reported that Favipiravir is effective against COVID-19[5].

Drugs can cause abnormalities in the hematopoietic system by affecting the leukocyte series, erythrocyte series, platelets, and the entire clotting system through various mechanisms[6]. We have relatively little clinical experience with favipiravir in this regard. Physicians should be aware of the potential hematologic complications due to the drugs used during the pandemic period. In animal studies related to treatment with favipiravir, its effect on various hematological parameters was studied[7-9]. In the literature, there was no study published in English about the effect of favipiravir on the hematological system in humans.

In this study, we aimed to retrospectively investigate the hematological parameters of patients receiving Favipiravir therapy, before and after the treatment.

METHODS

Sixty-two cases receiving favipiravir treatment for at least five days between March 25, 2020, and May 5, 2020, due to COVID-19 infections were evaluated retrospectively. Age, gender, nasopharyngeal swab positivity, findings from computerized tomography (CT) of the thorax, chronic diseases, intensive care unit or service admission, and other demographic parameters of the patients were analyzed. Patients with hematological coagulation and hematologic parameters, such as white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Htc), neutrophil, lymphocyte, platelet, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) before and after treatment, and those with an oncological disease, with a history of chemotherapy, receiving warfarin therapy or receiving medications simultaneously to favipiravir, or known to have hematologic side effects were excluded from the study.

Hemogram measurement

Hematologic analysis of the patients was performed by taking 24 parameters from the Cell Dyn 3700 brand hemogram device (Abbott, USA). Two-ml blood samples were taken from each patient via venipuncture and delivered to the laboratory for study within 2 hours.

Sample collection and Nükleic Acid Isolation And Reverse Transcription Polymerase Chain Reaction (RT-PCR) Study

Bio-Speedy® Viral Nucleic Acid Isolation Kit (Bioeksen, Turkey) was used for total nucleic acid isolation from the specimens. Bio-Speedy® COVID-19 RT-qPCR Detection Kit (Bioeksen, Turkey) was used for the RT-PCR assays. The PCR amplification and evaluation of the results were carried out according to the recommendations of the manufacturer.

Ethics: An ethics committee approval from Sakarya University Medical Faculty was provided for this study.

Statistical Analysis: Quantitative data were expressed as mean values ± SD, medians, and ranges. Qualitative data were expressed as numbers and percentages. The assumption of normality was tested by the Kolmogorov-Smirnov test. Paired Samples T-test and Wilcoxon Signed Rank tests were used when appropriate. A p-value of less than 0.05 was considered statistically significant. Analyses were performed by using Statistical Package for the Social Sciences version 20.0 (IBM SPSS Statistics; Armonk, NY, USA).

RESULTS

The mean age of the patients receiving favipiravir due to COVID-19 infections was 63.7±12.3 years, and 36 (58.1%) were male. Forty-five (72.6%) patients with mild or moderate illness were followed-up in the ward, while 17 (27.4%) patients with severe illness were followed-up in the intensive care unit. COVID-19 RNA test was positive in a nasopharyngeal swab test in 42 (67.7%) patients. The most common comorbid conditions found in patients were hypertension in 25 (40.3%), diabetes mellitus in 16 (25.8%), and smoking history in 8 (12.9%) patients. Thorax CT findings were detected in 58 patients as bilateral and in 4 as unilateral involvement (Table 1, Figure 1).

In the statistical analysis of hematological

parameters before and after favipiravir, WBC, prothrombin time, activated partial thromboplastin time, and international normalized ratio (PT-PTT-INR) levels were found to be unaffected (p=0.141, 0.503, 0.111, 0.245, respectively); while the mean RBC was found to be decreased from 4.33 ± 0.58 M/uL to 4.16 ± 0.54 M/uL (p=0.003); the median Hb level was found to be decreased from 12.3 g/dl to 11.9 g/dl (p=0.041); Htc level was decreased from 38.1% ± 4.8 to 36.9% ± 4.2 (p=0.026); the median neutrophil count was decreased from 4.57 K/uL to 3.85 K/uL (p=0.001); the mean lymphocyte count was found to be increased from 1.22 ± 0.53 K/uL to 1.84 ± 1.19 K/uL (p=0.000); the mean platelet count was found to be increased from 244.1 ± 85.1 K/uL to 281.9 ± 103.3 K/uL (p=0.005) statistically (Table 2, Figure 2).

TABLE 1. THE BASELINE CHARACTERISTICS OF PATIENTS WHO USED FAVIPIRAVIR

Parameters	Value
Age (Years) mean values ± SD (min.-med.-max.)	63.7±12.3 (37.0 – 64.0 – 89.0)
Sex (F/M) (%)	26/36 (41.9/58.1)
Nasopharyngeal swab positivity (-/+) (%)	20/42 (32.3/67.7)
Number of intensive care unit patients	17 (%27.4)
Thorax CT Findings (bilateral-unilateral infiltration)	58 (%93.5)/ 4 (%6.5)
Comorbid Condition Smoking Hypertension Diabetes Mellitus Heart disease COPD Asthma	Frequency (%) 8 (12.9) 25 (40.3) 16 (25.8) 4 (6.5) 2 (3.2) 4 (6.5)

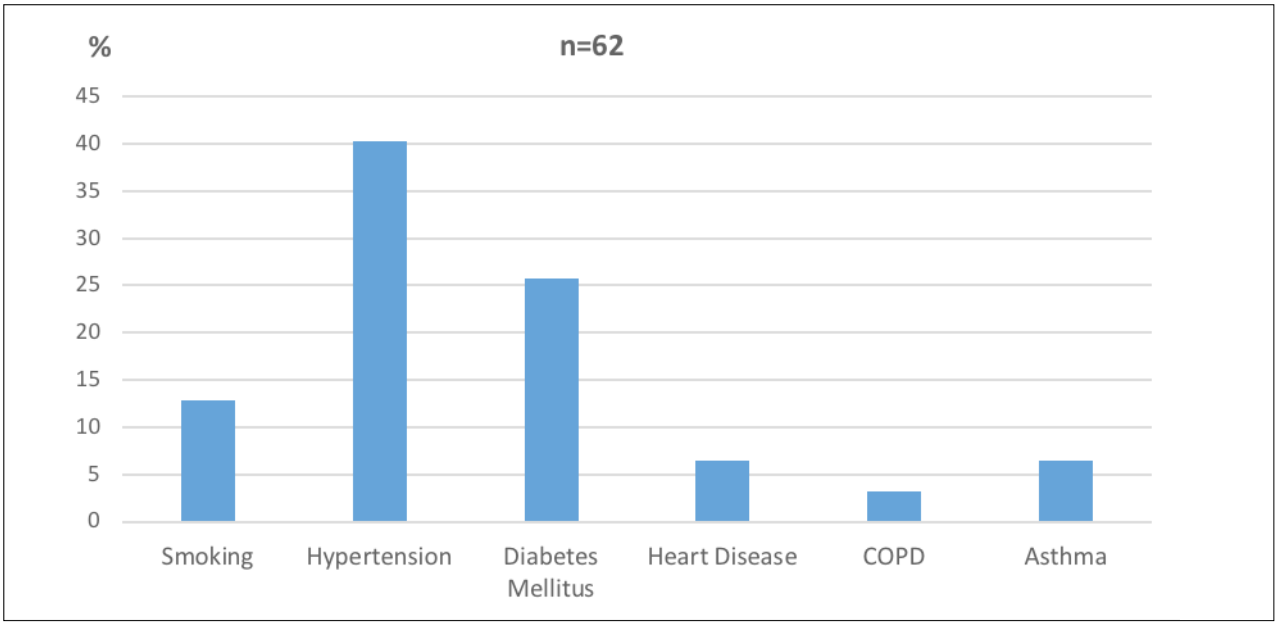
COPD: Chronic obstructive pulmonary disease

TABLE 2. COMPARISON OF THE HEMATOLOGICAL PARAMETERS OF PATIENTS BEFORE AND AFTER FAVIPIRAVIR TREATMENT

Parameters	Before favipiravir treatment mean ± SD(min.-med.-max.)	After favipiravir treatment mean ± SD (min.-med.-max.)	p
WBC (K/uL)	7.13 ± 3.27 (1.97 – 6.58 – 20.50)	6.59 ± 2.52 (0.67 – 6.58 – 20.50)	0.141*
RBC (M/uL)	4.33 ± 0.58 (3.01 – 4.34 – 5.48)	4.16 ± 0.54 (3.24 – 4.12 – 5.82)	0.003*
Hb (g/dl)	12.1 ± 1.6 (9.0 – 12.3 – 15.6)	11.8 ± 1.3 (9.2 – 11.9 – 14.5)	0.041**
Htc (%)	38.1 ± 4.8 (28.1 – 38.3 – 48.3)	36.9 ± 4.2 (28.1 – 37.0 – 46.1)	0.026*
Leu (K/uL)	1.22 ± 0.53 (0.35 – 1.23 – 3.05)	1.84 ± 1.19 (0.26 – 1.62 – 8.20)	0.000*
Neu (K/uL)	5.28 ± 2.98 (1.10 – 4.57 – 17.70)	4.21 ± 1.85 (1.62 – 3.85 – 10.10)	0.001**
Plt (K/uL)	244.1 ± 85.1 (81.0 – 230.0 – 460.0)	281.9 ± 103.3 (41.9 – 276.0 – 580.0)	0.005*
PT (sekond)	12.9 ± 1.3 (10.1 – 12.8 – 17.3)	12.9 ± 2.2 (10.3 – 12.5 – 25.8)	0.503**
PTT (sekond)	24.9 ± 2.7 (20.8 – 24.5 – 33.5)	25.9 ± 3.8 (18.7 – 25.3 – 41.6)	0.111*
INR	1.16 ± 0.15 (0.50 – 1.17 – 1.59)	1.15 ± 0.14 (0.70 – 1.14 – 1.61)	0.245**

* Paired Samples T-Test was used.** Wilcoxon Signed Rank Test was used.
White Cell Count (WBC): NV: 4.6-10.2 (K/uL), Lymphocyte Count (Leu): NV: 0.6-3.4 (K/uL), Platelet Count (Plt): NV: 142-424 (K/uL), Neutrophil Count (Neu): 2-6.9 (K/uL), Red Blood Cell ount (RBC): NV: 4-6.1 (M/uL), Hemoglobin (Hb): NV: 12.2-18.1 (g/dl), Hematocrit (Htc): NV: 37.7-53.7 (%), Prothrombin time (PT): NV: 7-12.9 (sekond), Activated Partial Thromboplastin Time (aPTT): NV: 18.5-33.5 (sekond), International Normalized Ratio (INR): NV: 0.8-1.3

FIGURE 1. COMORBID CONDITIONS OF PATIENTS WHO USED FAVIPIRAVIR



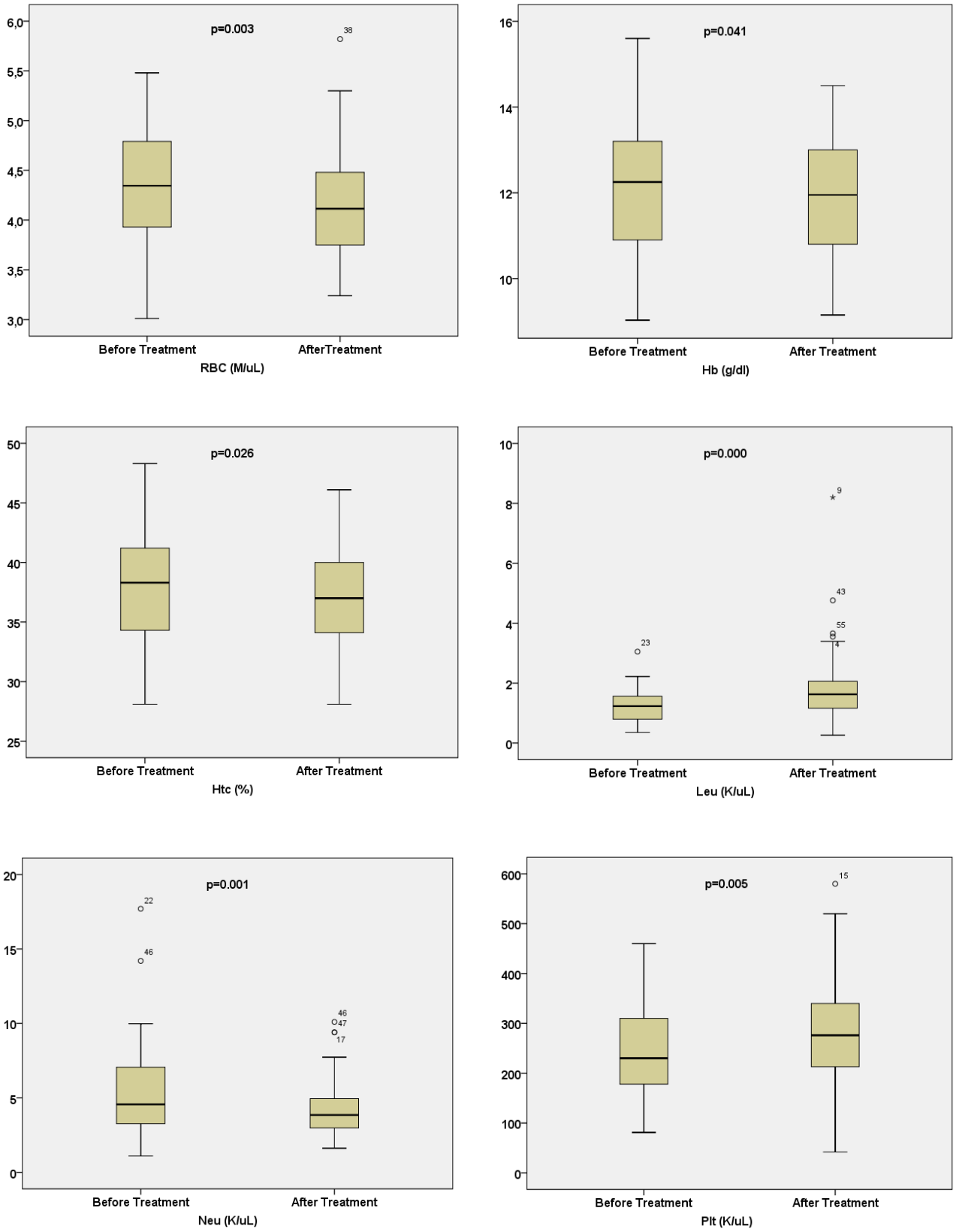


FIGURE 2. COMPARISON OF THE STATISTICALLY SIGNIFICANT HEMATOLOGICAL PARAMETERS OF THE PATIENTS BEFORE AND AFTER FAVIPIRAVIR TREATMENT

DISCUSSION

COVID-19 has caused a significant outbreak throughout the world and has challenged health care systems. Many pharmacological agents are used in its treatment, one of which is favipiravir[5]. Favipiravir was originally developed for influenza treatment, acting as a chain terminator at the point of binding of the viral RNA and reducing the viral load[4]. In addition to influenza, favipiravir has a wide spectrum of in-vitro anti-RNA virus activity and activities in deadly RNA viruses[4,5,10].

Hematologic system side effects associated with various antivirals have been reported in the literature[6]. For instance, one study found that anemia was significantly reduced after antiretroviral treatment, without any significant changes in other elements of the series[11]. In a different article, ribavirin, which is used together with peginterferon for the treatment of hepatitis C, was associated with anemia[12]. In another work, pure red cell aplasia was reported due to lamivudine used for human immunodeficiency virus (HIV) treatment and ribavirin used for hepatitis C treatment[13,14]. Another case report discusses thrombocytopenia development due to antiviral treatments for hepatitis C (daclatasvir and asunaprevir)[15].

Adverse effects on hematopoietic tissues such as elongation in PT, decreased myelopoiesis, decrease in erythrocyte series (RBC, Hb, Htc), and decrease in lymphocytes have been reported in toxicity studies conducted with animal experiments after oral favipiravir administration[16]. In another study, thrombocytopenia and coagulation parameters were found to be increased, although not significantly, as hematologic side effects[7,9]. In one mice study, there were no significant statistical differences in favipiravir hemogram parameters compared to the control group; but a decrease in the lymphocyte count and an increase in the neutrophil count were found in infected mice, compared to non-infected ones[8]. In another study, favipiravir was shown to prevent leukopenia and thrombocytopenia developed due to severe infection[17].

There were no studies in the literature investigating hematological parameters related to favipiravir treatment in humans. According to the literature data, lymphocyte and platelet levels in severe COVID-19 infections are lower than in mild COVID-19 infections and are indicated as a severity criterion for the disease[18,19]. Also, thrombocytopenia was shown to be associated with mortality in COVID-19 patients[20]. The results of our study showed that WBC, PT, PTT, and INR levels were unchanged after favipiravir use, RBC, Hb, htc, and neutrophil levels were decreased significantly ($P<0.05$), while lymphocyte and platelet levels were increased significantly ($P<0.05$). Considering the tendency of increase of platelet and lymphocyte levels after favipiravir treatment, as detected in our results, and since those parameters were shown to be severity criteria and mortality indicators in the literature, it can be stated that treatment with favipiravir has a positive effect on the hematologic parameters in COVID-19 patients.

According to our findings, suppression of the erythrocyte series was observed in the bone marrow with the use of favipiravir. Therefore, regular hemogram follow-up is required in patients using this medication. However, the positive effect of favipiravir on lymphocytes, neutrophils, and platelets should not be ignored.

LIMITATIONS: The low number of cases included in the study, its single-centered nature, and the short follow-up period can be considered limitations.

CONCLUSION

Favipiravir therapy used in the treatment of COVID-19 showed suppression of the erythrocyte series and a tendency to increase platelets. A therapeutic effect was observed on thrombocytopenia and lymphopenia, which are considered severity criteria and mortality predictor factors for this disease. Also, due to the limited information about treatment with favipiravir in COVID-19 patients, we believe that our findings will contribute significantly to the literature.

Author's Contribution

SY: Data collection, Data analysis and interpretation, Conception or design of the work, drafting the article, critical revision of the article, final approval of the version.

HD: DŞ; ABG; HK; DÇ: Data collection, Conception or design of the work, data analysis and interpretation, critical revision of the article, final approval of the version.

CV; AA; MK; OK: Data analysis and interpretation, final approval of the version to be published.

RESUMO

INTRODUÇÃO: *Este estudo tem como objetivo avaliar as alterações nos parâmetros hematológicos após o acompanhamento de pacientes que receberam tratamento com favipiravir devido à infecção por Covid-19.*

MÉTODOS: *Sessenta e dois casos em tratamento com favipiravir por pelo menos cinco dias devido à infecção por Covid-19 foram avaliados retrospectivamente. Parâmetros como idade, sexo, positividade do swab nasofaríngeo e doenças crônicas foram analisados. Os parâmetros hematológicos foram analisados antes e após o tratamento.*

RESULTADOS: *A idade média dos pacientes que receberam tratamento com favipiravir foi de 63,7±12,3 anos. A positividade do swab nasofaríngeo foi detectada em 67,7%. As condições comórbidas mais comuns detectadas nos pacientes foram hipertensão em 25 casos (40,3%) e diabetes em 16 casos (25,8%). Na análise estatística dos parâmetros hematológicos antes e após o tratamento com favipiravir, os níveis de leucócitos, PT-PTT-INR não foram afetados. Verificou-se que o RBC médio diminuiu de 4,33±0,58 M/uL para 4,16±0,54 M/uL (p=0,003); o nível médio de hemoglobina foi reduzido de 12,3 g/dl para 11,9 g/dl (p=0,041); o nível de hematócrito diminuiu de 38,1%±4,8 para 36,9%±4,2 (p=0,026); a contagem mediana de neutrófilos diminuiu de 4,57 K/uL para 3,85 K/uL (p=0,001); a contagem média de linfócitos aumentou de 1,22±0,53 K/uL para 1,84±1,19 K/uL (p=0,000); a contagem média de plaquetas aumentou de 244,1±85,1 K/uL para 281,9±103,3 K/uL (p=0,005).*

CONCLUSÃO: *Concluiu-se que o efeito patológico do tratamento com favipiravir no sistema hematológico foi a supressão na série eritrocitária e que não houve efeitos adversos em outros parâmetros hematológicos.*

PALAVRAS-CHAVE: *Infecções por coronavírus. Antivirais. Sangue. Células sanguíneas. Favipiravir.*

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Regarding the article "The effects of favıpıravır on hematologıcal parameters of covıd-19 patıents" with DOI number: http://dx.doi.org/10.1590/1806-9282.66.S2.65, published in Journal of the Brazilian Medical Association, 2020;66(SUPPL 2), page 65, Author's Contribution changed:

From: The authors contributed equally to the work.
To: SY: Data collection, Data analysis and interpretation, Conception or design of the work, drafting the article, critical revision of the article, final approval of the version.
HD: DŞ; ABG; HK; DÇ: Data collection, Conception or design of the work, data analysis and interpretation, critical revision of the article, final approval of the version.
CV; AA; MK; OK: Data analysis and interpretation, final approval of the version to be published.