ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):339-345
DOI: 10.4274/BMB.galenos.2021.07.084

Results of Favipiravir Combined Treatment in Intensive Care Patients with COVID-19

COVID-19 Tanılı Yoğun Bakım Hastalarında Favipiravir Kombine Tedavisinin Sonuçları

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) is a disease that has already taken place in human history. Although there is still no effective treatment 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.

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

Results: The average age of the study group was 60.9±16.4 years and 65.9% (n=118) of them were male. According to the clinical classification, more than half (50.8%, n=91) were included in the "high" clinical classification. The most common chronic disease was "hypertension (HT)" (42.5%, n=76) and the most common symptom was "fever" (57.5%, n=103). While 82.7% (n=148) had widespread computed tomography findings, C-reactive protein (CPR) positivity rate was 65.4% (n=117). Statistically significant difference was detected among three measurements of blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, CRP between during admisson, the 1st and the 3rd days.

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) insanlık tarihinde çoktan yerini almış bir hastalıktır. Halen etkili bir tedavi protokolü bulunmamakla birlikte farklı tedavi seçenekleri denenmektedir. Bu çalışmada yoğun bakım ünitesine COVID-19 tanısıyla yatırılan ve favipiravir içeren tedavi protokolü uygulanan hastaların temel özelliklerinin ve laboratuvar bulgularındaki değişikliklerin belirlenmesi amaçlanmıştır.

Yöntem: Çalışma 01.06.2020-30.06.2020 tarihleri arasında yoğun bakım ünitesinde yatan 179 hastanın verileriyle gerçekleştirilmiştir. Çalışmaya dahil edilme kriterleri; polimeraz zincir reaksiyon testi ile doğrulanmış COVID-19 tanısına sahip olmak, yoğun bakım ünitesinde yatırılmak, favipiravir ile kombine tedavi almak ve otomasyon sistemi üzerinden verilerine erişilebilmektir. Literatüre göre hastaların sosyo-demografik özellikleri, bazı temel özellikleri ve bazı laboratuvar bulguları değerlendirilmiştir. İstatistiksel analiz SPSS (Statistical Package for Social Sciences) versiyon 24.0 (IBM Corp.; Armonk,NY,ABD) kullanılarak yapılmıştır.

Bulgular: Çalışma grubunun yaş ortalaması 60,9±16,4 yıl olup, %65,9'u (n=18) erkektir. Klinik sınıflandırmaya göre yarıdan fazlası (%50,8, n=76) "yüksek" klinik sınıflandırmaya dahil edilmiştir. En sık görülen kronik hastalık "hipertansiyon" (%42,5, n=76) ve en sık görülen semptom "ateş"tir (%57,5, n=103). %82,7'sinde (n=148) yaygın bilgisayarlı tomografi bulguları bulunurken, C-reaktif protein (CPR) pozitiflik oranı %65,4'tür (n=117). Başvuru sırasında, birinci ve üçüncü günler arasında üç kan üre nitrojen, aspartat aminotransferaz, alanin aminotransferaz, CRP ölçümleri arasında istatistiksel olarak anlamlı bir fark tespit edilmiştir.

Sonuç: Favipiravir uygun bir güvenlik profili göstermektedir. Ancak yan etkileri, teratojenitesi, hiperürisemi ve düzeltilmiş QT aralığı uzaması

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Cite this article as: Yılmaz H, Güner AE, Altuntaş M. Results of Favipiravir Combined Treatment in Intensive Care Patients with COVID-19. Bagcilar Med Bull 2021;6(3):339-345

Abstract

Conclusion: Favipiravir demonstrates a proper safety profile. However, its side effects including teratogenicity, hyperuricemia 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.

Keywords: COVID-19, favipiravir, laboratory findings, side effect, treatment

Öz

henüz yeterince araştırılmamıştır. Kısa süreli kullanımda güvenli ve tolere edilebilir olabilir; ancak tedavinin uzun dönem etkilerini değerlendirmek için daha fazla kanıt gerekmektedir.

Anahtar kelimeler: COVID-19, favipiravir, laboratuvar bulguları, tedavi, yan etkiler

Introduction

In the twenty first 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 Coronavirus disease-2019 (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, also 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 (HT), 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 or angiotensin II receptor blocker in the early period is also recommended (8). Despite all these, 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 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 have 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 1.600 mg twice daily (first day), 600 mg twice daily (days 2-5) and it is 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* are 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.

Materials and Methods

The study was planned in a retrospective, cross-sectional way. It was carried out with the data of inpatients at the University of Health Sciences Turkey, İstanbul Göztepe Training and Research Hospital Adult Intensive Care Unit between 01.06.2020 and 30.06.2020. The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Göztepe Training and Research Hospital, Turkey 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.

The inclusion criteria of the study are to have a diagnosis of COVID-19 confirmed by polymerase chain reaction (PCR) test, to be hospitalized in the intensive care unit, to be receiving favipiravir combined therapy and to have access to its data through the automation system. The study included data from 179 patients who met these criteria.

According to literature, the socio-demographic characteristics, some basic characteristics and some laboratory findings of the patients were obtained from the hospital computer records. Clinical status of the patients were classified as mild, moderate and high.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA). Means and standard deviations are given for the variables obtained by measurement, number and percentage distributions for the data obtained by counting. The 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.

The 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.

Results

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

Table 1. Basic characteristics of the patients

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

PCR: Polymerase chain reaction

Laboratory measurements were carried out on adimission to the intensive care hospitalization, on the 1st day and on the 3rd day.

The values of all patients who were admitted to the intensive care unit (ICU) and treated with favipiravir/favipiravir + tosilizumab given in Table 2. They were compared on the day of admission to the intensive care unit and 1st and 3rd days days of hospitalization and statistically significant difference was found for BUN (p=0.000), AST (p=0.029), ALT (p=0.001), CRP (p=0.001), ferritin (p=0.024) and D-dimer (p=0.000) (Table 2).

AST, ALT and D-dimer values increased in a statistically significant way in patients receiving favipiravir/favipiravir + tosilizumab treatment. It was seen that CRP and ferritin values increased on the 1st day and decreased on the 3rd day (Table 2).

The values of the patients treated with only favipiravir were given in Table 3. The BUN, ALT, CRP and D-dimer values of patients who were admitted to ICU and treated with favipiravir were compared on the day of admisson, day 1 and day 3 and a statistically significant difference was found for BUN (p=0.000), ALT (p=0.000), CRP (p=0.000) and D-dimer (p=0.000)]. ALT and D-dimer values increased significantly while CRP value increased on day 1 and decreased on day 3 (Table 3).

The values of the patients treated with favipiravir/tocilizumab combination were given in Table 4. Creatinine, ALT, CRP, ferritin and D-dimer values were compared on the admission, and days 0 and 3 of hospitalization in patients who were admitted to ICU and treated with combination of favipiravir and tocilizumab, and a statistically significant difference was found for creatinine (p=0.000), ALT (p=0.03), CRP (p=0.004), ferritin (p=0.03) and D-dimer (p=0.01). ALT and ferritin values increased significantly while CRP and D-dimer increased on day 1 and decreased on day 3 (Table 4).

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 emphasizes recovery two days after favipiravir treatment. This case suggests 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 ≥60 years of age. The ≥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 varied 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 present study.

Table 2. Comparison of laboratory findings on hospitalization, 1st and 3rd days of treatment (favipiravir/favipiravir+tosiluzimab) in intensive care patients

Laboratory findings	Day 0	Day 1	Day 3	p	Days 0/1	Days 0/3	Days 1/3
Leukocyte	8.03±4.28	8.1±4.22	8.31±4.51	0.270	0.300	0.082	0.159
Lymphocyte	1.29±0.93	1.19±0.84	1.22±0.78	0.590	0.203	0.858	0.433
BUN	42.96±28.77	42.07±33.24	42.71±36.87	0.000	0.006	0.095	0.682
Creatinine	1.33±1.13	1.35±1.33	1.33±1.05	0.110	0.007	0.515	0.522
AST	47.51±151.69	57.97±255.23	63.19±167.83	0.029	0.015	0.020	0.199
ALT	38.51±47.49	43.4±63.79	69.41±17197	0.001	0.081	0.000	0.000
CRP	81.02±74.86	114.9±78.21	89.81±79.5	0.001	0.000	0.269	0.000
Procalcitonin	1.18±3.09	2.12±9.12	2.77±11.36	0.099	0.030	0.388	0.059
Ferritin	1049.46±3642.29	1227.22±3574.8	1177.04±3108.04	0.024	0.000	0.001	0.449
D-dimer	1279.79±2589.74	2057.72±4252.65	2201.09±3693.58	0.000	0.008	0.000	0.019
Fi-O_2	45.7±28.62	53.85±25.91	54.8±26.83	0.680	0.206	0.213	0.445
Pa-O_2	70.44±27.65	68.23±30.24	82.72±24:9	0.480	0.109	0.866	0.088

*Hosp. means hospitalization, CRP: C-reactive proetin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

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 HT or diabetes (15). Three registered clinical trials are planned regarding the use of favipiravir against COVID-19 (16-18). The presented study was performed in an intensive care unit and parallel to the mentioned studies; 42.5% of the patients (n=76) had HT and 29.1% (n=52) had diabetes mellitus.

In the present study, the most common symptom was ''fever'' (57.5%, n=103) and second symptom was dyspnea (42.5%, n=76). In a similar study, the 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 rhinorrhea (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

Table 3. Comparison of the laboratory findings of favipiravir treatment in hospitalized patients on admission, day 1 and day 3, in intensive care unit

Laboratory findings	Day 0	Day 1	Day 3	p	Days 0/1	Days 0/3	Days 1/3
Leukocyte	7.8±4.22	7.89±4.01	8.12±4.1	0.27	0.48	0.11	0.13
Lymphocyte	1.31±0.95	1.2±0.87	1.25±0.79	0.39	0.10	0.68	0.23
BUN	44.14±30.32	42.92±34.69	43.2±37.42	0.00	0.00	0.06	0.48
Creatinine	1.35±1.21	1.37±1.41	1.36±1.06	0.37	0.04	0.84	0.45
AST	49.67±163.89	61.12±275.89	63.29±181.04	0.23	0.04	0.19	0.60
ALT	38.32±50.78	42.51±67.27	68.03±185.33	0.00	0.33	0.00	0.00
CRP	80.83±73.25	111.68±74.85	85.88±75.68	0.00	0.00	0.69	0.00
Procalcitonin	0.81±1.79	2.28±9.97	3.29±12.65	0.20	0.06	0.27	0.02
Ferritin	1088.98±3916.67	1236.21±3849.44	1169.39±3345.06	0.10	0.00	0.02	0.66
D-dimer	1374.14±2774.97	1822.96±3204.11	2035.12±3405.97	0.00	0.06	0.00	0.02
Fi-O_2	45.73±29.09	53.28±26.55	55.31±28.13	0.79	0.40	0.33	0.68
Pa-O_2	70.67±28.61	71.89±31.1	86.64±26.32	0.74	0.18	0.87	0.40

*Hosp. means hospitalization, CRP: C-reactive proetin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 4. Comparison of laboratory findings on admission and days 1 and 3 of hospitalization in intensive care patients who received favipiravir and tosilizumab treatment together

Laboratory findings	Day 0	Day 1	Day 3	p	Days 0/1	Days 0/3	Days 1/3
Leukocyte	9.64±4.46	10.71±5.89	10.41±5.98	0.59	0.360	0.465	0.897
Lymphocyte	1.17±0.73	1.29±0.69	1.12±0.7	0.61	0.505	0.623	0317
BUN	37.71±15.68	38.06±16.78	38.29±19.62	0.98	0.783	0.906	0.653
Creatinine	1.21±0.33	1.06±0.24	1±0	0.00	0.018	0.012	0.317
AST	40.06±17.94	49.29±25.32	70.06±54.12	0.00	0.099	0.002	0.058
ALT	43.06±19.13	60.47±41.65	76.88±40.66	0.03	0.019	0.003	0.193
CRP	96.07±89.2	161.24±94.3	144.12±95.35	0.01	0.004	0.028	0.523
Procalcitonin	2.67±7.01	1±2	0.64±1.34	0.43	0.225	0.893	0.317
Ferritin	1121.31±1220.96	1499.67±1120.54	1551.25±1524.33	0.03	0.310	0.038	0.331
D-dimer	840.21±724.47	4877.38±9598.96	4230.18±5685.62	0.01	0.017	0.003	0.679
Fi-O_2	40.5±27.58	71.25±8.54	62.5±9.57	0.36	0.317	0.542	0.180
Pa-O_2	67±0	51.75±21.79	69±13.78	0.37	0.572	0.624	0.068

*Hosp. means hospitalization, CRP: C-reactive proetin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

study that reports prolonged QT interval due to favipiravir has been encountered (19). In another study, two patients who were followed up in the ICU with favipiravir combined treatment developed ventricular tachycardia; both had increased T peak to T end (Tp-e) interval and Tp-e/corrected QT interval (QTc) ratio despite normal QTc intervals before the treatment (21). In the present 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 to favipiravir or favipiravir/ticilizumab combined treatment group. In another study, favipiravir had significantly fewer adverse effects than the lopinavir/ritonavir group (22). Similarly, a 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 women should not be treated with favipiravir (25). In the presented study, serum uric acid levels were not evaluated but liver enzyme abnormalities were detected in parallel to the literature.

In a prospective, single-arm and multicenter study conducted in Italy with 63 patients with severe COVID-19, a decrease in CRP, ferritin and D-dimer levels was observed after tocilizumab treatment (27). In our study, when the laboratory values of the 3rd day were examined, it was observed that the D-dimer level increased in patients who received only favipiravir treatment, while the level of D-dimer decreased in those who received favipiravir+tocilizumab treatment. In a study conducted with 23 patients who had severe COVID-19 and were hospitalized in ICU in Turkey, it was shown that CRP and ferritin values decreased while D-dimer values increased after tocilizumab treatment (27).

Conclusion

Favipiravir demonstrates a proper safety profile. However, its side effects including teratogenicity, hyperuricemia 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.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Göztepe Training and Research Hospital, Turkey with the decision number 2020/0243.

Informed Consent: The study was designed retrospective.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Y., Desing: H.Y., Data Collection or Processing: H.Y., Analysis or Interpretation: H.Y., M.A., Drafting Manuscript: H.Y., A.E.G., Critical Revision of Manuscript: H.Y., A.E.G., Final Approval and Accountability: H.Y., A.E.G., M.A., Technical of Material Support: H.Y., A.E.G., M.A., Supervision: H.Y., A.E.G., M.A.

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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