ORIGINAL RESEARCH

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Evaluation of Clinical Features of Patients Diagnosed with MIS-C

MIS-C Tanısıyla Takip Edilen Hastalarımızın Klinik Özelliklerinin Değerlendirilmesi

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Abstract

Objective: Evaluation of clinical features and results in multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease-2019.

Method: Patients diagnosed with MIS-C between September 1, 2020 and February 25, 2021, followed at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Pediatrics were included. Their clinical findings and laboratory results were evaluated retrospectively.

Results: The average age of 16 patients diagnosed with MIS-C was found to be 6.5 years; of them, 62.5% were male and 37.5% were female. Our patients had no chronic disease. Fever (100%) and stomachache (81.25%) were the most common symptoms. All patients had high levels of C-reactive protein, procalcitonin, D-dimer and pro-brain natriuretic peptide at the time of diagnosis. The average ejection fraction was found as 63.1% in echocardiography. Intravenous immunoglobulin, corticosteroids and acetylsalicylic acid were administered to all patients whereas enoxaparin and vasopressors were administered to 11 (68.75%) and 3 (18.5%) patients, respectively. Left ventricular ejection fraction was found to be within the normal range at all patients at the time of discharge. The average in patient follow-up was found to be 10 days.

Conclusion: It is important to have a long-term follow-up of MIS-C patients, who show similar symptoms to Kawasaki disease and yet have their own particular symptoms and cardiac involvement, in order not to miss the opportunity of early diagnosis as well as cardiac complications.

Keywords: COVID-19, MIS-C, pediatrics

Öz

Amaç: Çalışmada kliniğimizde izlediğimiz çocuk hastalarda koronavirüs hastalığı-2019 ile ilişkili multisistem enflamatuvar sendromunun (MIS-C) klinik özellikleri ve sonuçlarının değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışmaya 01/09/2020-25/02/2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi, Pediyatri Kliniği'nde takip edilen MIS-C'li çocuklar dahil edildi. Hastaların klinik özellikleri ve laboratuvar bulguları retrospektif olarak değerlendirildi.

Bulgular: MIS-C'li 16 çocuğun ortalama yaşı 6,5 yaş olup; %62,5'i erkek, %37,5'i kızdı. Hastalarımızın kronik hastalıkları yoktu. Ateş (%100) ve karın ağrısı (%81,25) en sık görülen semptomlardı. Tüm hastalarda C-reaktif protein, prokalsitonin, D-dimer ve pro-B-tipi natriüretik peptid seviyeleri tanı anında yüksekti. Ekokardiyografide ortalama ejeksiyon fraksiyonun %63,1 olduğu görüldü. Tedavi için intravenöz immünoglobulin, kortikosteroid, aspirin tüm hastalara verilirken, enoksaparin 11 (%68,75) ve vazopressörler 3 (%18,5) hastaya verildi. Hastalarımızın taburculuk öncesi yapılan kontrol ekokardiyografilerinde sol ventrikül ejeksiyon fraksiyonunun normal olduğu görüldü. Hastalarımız ortalama 10 gün yatırılarak izlendi.

Sonuç: Kawasaki hastalığı ile benzerlikler gösteren ancak kendine özgü özellikleri olan ve kardiyak tutulumla seyreden MIS-C'nin, klinik bulgularının atlanmaması, erken tanı konulup tedavi edilmesi önemlidir.

Anahtar kelimeler: COVID-19, MIS-C, pediyatri

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Introduction

By the end of January 2020, World Health Organization identified coronavirus disease-2019 (COVID-19) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection as pandemic (1). COVID-19 is known to be affecting the respiratory system predominantly, with wide range of clinical features including mild upper respiratory system symptoms to severe acute respiratory distress syndrome (2,3).

By the end of April 2020, a new clinical feature was reported by the United Kingdom, as an hyperinflammation syndrome, similar to Kawasaki disease (KD) with multiple organ involvement. This clinical identification was used in describing children who were recently or currently diagnosed with COVID-19 infection with no known chronic disease (4). These reported cases directed pediatricians to investigate the possible linkage between multisystem inflammatory syndrome in children (MIS-C) and KD (4).

Following the first case reports from UK, similar cases were reported from several European countries and USA (4-8). On May 14th 2020, United States Centers for Disease Control and Prevention (CDC) reported a clinical description for MIS-C (9).

According to this report, MIS-C is described as patients under 21 years of age, with proof of COVID-19 infection or contact with someone who had COVID-19 4 weeks prior to first symptoms, together with persistent fever, and severe illness requiring hospitalization with increased inflammatory markers in laboratory findings and at least 2 system involvement with no other possible diagnosis but post-viral immune mediated multisystem clinical manifestation (9).

The data with regard to clinical and epidemiologic features of patients with MIS-C are still limited. In the reported cases, most common symptoms are nausea and vomiting, stomach pain and diarrhea, which are all related to gastrointestinal system involvement (4-6). Mucocutaneus involvement similar to KD headache, irritability and encephalopathy due to nervous system involvement and hypotension, and decreased ventricular function due to cardiac involvement are amongst other symptoms. In contrary to KD, coronary artery involvement is known to be rarer (4-6).

MIS-C is a clinical status in children due to COVID-19 infection, with no certain protocol in follow-up or treatment. Studies with regard to clinical and laboratory findings should continue in order to distinguish this particular disease. In this retrospective case series, we share our clinical experience of following and treating 16 patients diagnosed with MIS-C.

Materials and Methods

Design of the Study

Retrospective evaluation of 16 patients between the ages of 1 month-18 years, followed at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Pediatrics between Sep 1, 2020, and Feb 25, 2021 was performed.

Case description was done according to CDC criteria (https://www.cdc.gov/mis/hcp/index.html). At least two organ system involvement and one or more increased inflammatory markers [C-reactive protein (CRP), erythrocyte sedimentation rate, fibrinogen, procalcitonin, ferritin, interleukin-6] were among the inclusion criteria. For viral proof, polymerase chain reaction (PCR) testing and IgG and IgM antibody tests against COVID-19 were done. Those who did not meet the criteria or those who were suspected to be ill without any proof were excluded from the study.

Currently, there is not any classification of the severity of the disease. The classification is done by vasoactive-inotropic score (VIS), requirement of respiratory support and laboratory findings (10). Because not every patient has the same organ system involvement, the clinical classification is done according to the system that is mostly affected.

In mild cases, the oxygen requirement is minimal, there is no need for inotropic agents and organ failure degree is minimal. In moderate cases, VIS is 10 or lower, obvious oxygen requirement and/or mild or isolated organ damage is present. In severe cases, VIS is greater than 10, invasive/non-invasive mechanical ventilation support and/or moderate or severe organ damage including ventricular dysfunction is present.

Data Collection and Analysis

Patients were divided into three groups depending on the clinical manifestation as mild, moderate and severe. The clinical, laboratory and radiologic data of the patients were gathered from official medical reports with a standardized data collection form. Medical consent forms were signed by the parents.

Statistical Analysis

Descriptive analyses were performed in order to provide information regarding the general characteristics of the

study groups. Data related to the continuous variables were given in the form of mean ± standard deviation and categorical variables were given as n (%).

Ethical approval was taken from the Ethical Board of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşçıoğlu Training and Research Hospital on 22/03/2021 with the registry number E-48670771-514.10.

Clinical Findings

The average age of 16 patients who were included in the study (10 male, 6 female) was found to be 6.5±1.66 years at the time of diagnosis. Our patients had no chronic illnesses. Twelve patients (75%) were Turkish citizens and 4 (25%) were Syrian. Height and weight percentile values were within the normal range.

Our patients were divided into three categories depending on the clinical status of their disease. Ten patients (62.5%) were included in the mild clinic class and followed at the pediatric isolation unit. Four patients (25%) were placed in the moderate category, and of them, 2 (50%) were followed at the pediatric isolation unit and the other 2 (50%) were followed at the pediatric intensive care unit. Two patients were included at the severe illness category (12.5%) and followed at the pediatric intensive care unit. Eleven of our patients (68.75%) had a history of COVID-19 PCR positive family member within the same household. One patient had positive COVID-19 PCR test at the time of diagnosis. All 16 patients had positive COVID-19 IgG test. All patients had fever (100%) at the time of arrival to the hospital and average fever time was found to be 4.6 days (3-7 days). The most common symptom was stomach pain (81.25%) (13/16) due to gastrointestinal system involvement. Other gastrointestinal system related symptoms were vomiting (43.75%) (7/16) and diarrhea (75%) (12/16). Of those who had stomach pain, 7 were consulted to pediatric surgery in regard to acute abdomen; however, no surgical involvement was required. Seven patients (43.75%) had acute non-purulent bilateral conjunctivitis, 4 patients had unilateral cervical lymphadenopathy (25%), and 8 patients (50%) had rash. Eight patients (50%) had strawberry tongue and peeling around their lips due to oral mucosa involvement. Four patients (25%) had headache as a result of neurologic involvement. Demographic characteristics and clinical symptoms are shown in Table 1.

At the time of diagnosis, 9 patients (56.25%) had pericardial effusion, 7 patients (43.45%) had mitral insufficiency, 2 patients (12.5%) had tricuspid insufficiency and 3 patients (18.75%) had left coronary artery involvement. The average ejection fraction (EF) of patients was found to be 63.1 (47-79), the average fractional shortening was 34.4 (27-46). During to control echocardiography on the third day of our inpatient follow-up, 4 patients (25%) still had pericardial effusion, 8 patients (50%) had mitral insufficiency, 2 patients (12.5%) had tricuspid insufficiency and 3 patients (18.75%) had left coronary artery involvement. Three patients had normal echocardiography results on day 3. The average EF was 71.4 (55-78), fractional shortening was 39.8 (29-46). In the echocardiography done on the day of discharge, 10 patients (62.5%) had normal results. One patient (3.25%) had left coronary artery enlargement and 5 patients (31.25%) had continuing mitral valve insufficiency. In the echocardiography done prior to discharge, the average EF and fractional shortening were reported as 74.1 (66-80) and 42.7 (36-50), respectively (Table 2).

Table 1. Demographic characteristics, clinical symptoms and COVID-19 test results

Patient characteristics	All patients (n=16)
Age (range)	6.5 (2.5-14.66)
Sex, n (%)	Male 10 (62.5), female 6 (37.5)
Citizenship, n (%)	
Turkish	12 (75)
Syrian	4 (25)
Chronic illness	0 (0)
Fever time, days (range)	4 (3-7)
Initial symptoms, n (%)	
Fever	16 (100)
Gastrointestinal findings	
Stomach pain	13 (81.25)
Vomiting	7 (43.75)
Diarrhea	12 (75)
Pediatric surgery consultation	7 (43.75)
Rash	8 (50)
Conjunctivitis	7 (43.75)
Hyperemia in the oral mucosa (strawberry tongue)	8 (50)
Peeling of lips	2 (12.5)
Myalgia	12 (75)
Headache	4 (25)
Cervical lymphadenopathy	4 (25)
Shortness of breath	3 (18.75)
COVID-19 contact, n (%)	11 (68.75)
COVID-19 test, n (%)	
COVID-19 antibody positive (IgG)	16 (100)
COVID-19 RT-PCR positive	1 (6.25)

COVID-19: Coronavirus disease-2019, RT-PCR: Reverse transcription-polymerase chain reaction

Table 2. Cardiovascular system examination of patients diagnosed with MIS-C

Patient characteristics	Prior to treatment (n=16)	3rd day of treatment (n=16)	At discharge from the hospital (n=16)
Echocardiography			
Normal, n (%)	0 (0)	3 (18.75)	10 (62.5)
Ejection fraction, average (range)	63.1 (47-79)	71.4 (55-78)	74.1 (66-80)
Shortness fraction, average (range)	34.4 (27-46)	39.8 (29-46)	42.6 (36-50)
Pericardial effusion, n (%)	9 (56.25)	4 (25)	0 (0)
Mitral valve insufficiency, n (%)	7 (43.75)	8 (50)	5 (31.25)
Tricuspid valve insufficiency, n (%)	2 (12.5)	2 (12.5)	0 (0)
Left coronary artery enlargement, n (%)	3 (18.75)	3 (18.75)	1 (6.25)

MIS-C: Multisystem inflammatory syndrome in children

The detailed laboratory findings of 16 patients included in the study are given in Table 3. At the time of admission, the average white blood cell count was found as 10.651 (4.03-22.7)×10^3/uL and at discharge, the average was 20.66 (9.86-48,4)×10^3/uL. Neutrophil count at the time of admission and discharge were 8.646 (3.09-20.95)×10^3/uL and 2.513 (2.99-30)×10^3/uL, respectively. The average lymphocyte counts were 1.534 (0.62-4.15)×10^3/uL upon admission and 6.481 (1.64-21.75)×10^3/uL at the time of discharge. The average thrombocyte count at admission and at discharge were 151.871 (20.95-308)×10^3/uL and 551,625 (241-859)×10^3/uL, respectively.

The level of blood sodium at admission was 128 (122-138) mmol/L, 136.5 (134-142) mmol/L on the third day and 136.1 (131-140) mmol/L at discharge. Albumin levels at admission and discharge were 3.3 (2.5-4.15) g/dL and 3.92 (3.2-4.97) g/dL, respectively. CRP level at admission was 158.6 (40-358) mg/L and 3.59 (0.26-4.4) mg/L at discharge. The average procalcitonin levels at admission and at discharge were 7.27 (0.29-12.92) ng/mL and 0.09 (0.02-0.24) ng/mL, respectively. The average ferritin level was 404 (228-2.000) ng/mL at admission and 201.19 (48-483) ng/mL at discharge. The average erythrocyte sedimentation rate was 36.8 (5-63) upon admission and 16.4 (3-46) at discharge. Amongst the cardiac enzymes, troponin-t levels at the time of admission and discharge were 131 (3.7-27,600) ng/L and 4 (2-6.89) ng/L, respectively, while pro-brain natriuretic peptide (BNP) levels were 7.153 (307-27,600) pg/mL during admission and 166 (52-458) pg/mL by the time of discharge. We had no patients with positive blood culture results.

At the time of admission, 11 patients (68.75%) had no pathological findings in their chest imaging. 4 patients (25%) had evidence of bilateral infiltration in the lower zones, coherent with pneumonia and 1 patient (6.25%) had ground-glass opacification. In the abdominal ultrasound imaging, 2 patients (12.5%) had no pathological finding whereas 14 patients (87.5%) had free fluid in the lower right quadrant (Table 4).

As the first line of treatment, all patients were administered a single dose of 2 gr/kg intravenous immunoglobulin (IVIg). There was no need for a second dosage. Glucocorticoid (2 mg/kg) was administered to 13 patients (81.25%) on the first day of treatment. Three patients (18.75%) were started on the glucocorticoid treatment with 10 mg/kg, and continued with 2 mg/kg. Acetylsalicylic acid 3-6 mg/kg (antiaggregant dose) was administered to all patients. D-dimer levels of 2 and higher was accepted as the indication of anticoagulation treatment (11). Eleven patients were started on enoxaparin treatment and continued until discharge. Three patients required inotropic medication and milrinone was added to their treatment. The average inpatient follow-up was 10 days (7-17) (Table 5).

Discussion

In the time of no standardized treatment protocol and fewer reported case series of patients diagnosed with MIS-C, our clinic followed 16 patients with a wide range of clinical presentation from stable to severe illness with decreased ventricular function.

Even though MIS-C was thought as a SARS-CoV-2 related KD, the data that surfaced since the initial diagnosis showed that MIS-C was a completely different clinical diagnosis. In contrary to KD being seen under the age of 5 years, in our study, MIS-C, in coherence with other case series, was found to be seen at the average age of 6.5 years (4,6).

All 16 patients who were accepted to our study had IgG antibody positivity against SARS-CoV-2 (COVID-19). The average time of contact with a person infected with

Table 3. Laboratory findings of patients with MIS-C

	Prior to treatment (n=16)	3rd day of treatment (n=16)	At discharge from the hospital (n=16)
Laboratory finding results, average (range)			
White blood cell (×10³/uL)	10.651 (4.03-22.7)	15.92 (9.86-48.4)	20.66 (9.86-48.4)
Neutrophil count	8.646 (3.09-20.95)	9.986 (3.21-30)	12.513 (2.99-30)
Lymphocyte count	1.534 (0.62-4.15)	4.318 (16.4-21.75)	6.481 (1.64-21.75)
Hemoglobin (g/dL)	10.99 (7-12.6)	10.83 (9.6-12.7)	11.94 (9.6-15)
Thrombocyte count (×10³/uL)	151.871 (20.95-308)	320.313 (128-719)	551.625 (241-859)
Serum sodium (mmol/L)	128 (122-138)	136.5 (134-142)	136.1 (131-140)
Serum creatinine (mg/dL)	0.58 (0.17-2.85)	0.31 (0.2-0.45)	0.33 (0.17-0.5)
Aspartate transaminase (U/L)	43.8 (15-164)	33.5 (22-57)	34.88 (18-57)
Alanine transaminase (U/L)	41.4 (8-187)	29 (8-57)	37 (16-165)
Albumin (g/dL)	3.3 (2.5-4.15)	3.11 (2.57-3.9)	3.92 (3.2-4.97)
Prothrombin time	16.3 (13.7-19.5)	13.43 (12-14.8)	12.82 (12-13.8)
Active partial thromboplastin time	31.6 (26-41)	27.93 (22-30.8)	25.45 (21.2-29)
International normalized ratio)	1.23 (1-1.47)	1 (0.88-1.1)	0.96 (0.89-1.03)
Fibrinogen (mg/dL)	597 (303-771)	371,5 (13.8-636)	287.6 (189-358)
C-reactive protein (mg/L)	15.6 (40-358)	43.34 (2.68-111)	3.59 (0.26-4.4)
Procalcitonin (ng/mL)	7.27 (0.39-12.92)	0.88 (0.11-2.85)	0.09 (0.02-0.24)
Ferritin (ng/mL)	404 (228-2.000)	330.69 (125-997)	201.19 (48-483)
D-dimer (ng/mL)	2.62 (0.8-4.49)	2.13 (0.9-4.6)	0.83 (0.31-1.78)
Troponin-T (ng/L)	131 (3.7-27,600)	61 (3-697)	4 (2-6.89)
Pro-BNP (pg/mL)	7153 (307-27,600)	5011 (131-35,000)	166 (52-458)
Erythrocyte sedimentation rate	36.8 (5-63)	23.69 (4-63)	16.4 (3-46)
Amylase (U/L)	45.8 (13-145)	-	-
Lipase (U/L)	36.1 (8-194)	-	-
Triglyceride (mg/dL)	268.25 (106-586)	-	-
Positive blood culture	0 (0)	-	-

MIS-C: Multisystem inflammatory syndrome in children, BNP: Brain natriuretic peptide

Table 4. Radiologic findings of patients with MIS-C

Patient characteristic	All patients (n=16)
Chest imaging, n (%)	
Normal	11 (68.75)
Ground-glass opacification	1 (6.25)
Bilateral lower zone infiltration	4 (25)
Abdominal ultrasound, n (%)	
Normal	2 (12.5)
Free fluid in the lower right quadrant	14 (87.5)

MIS-C: Multisystem inflammatory syndrome in children

COVID-19 was found to be 4.9 weeks prior to illness. Only 1 patient had positive RT-PCR positivity. This finding and the IgG antibody positivity showed that the disease started slowly, depending on the immune reaction of the patient (5).

Fever, being the common symptom in all 16 patients, was found to be parallel with other case series. Gastrointestinal system involvement was very common and seen in 15 patients and similar to the literature (12).

The mechanism of myocardial involvement is unclear: however, since MIS-C presents following the antibody formation against COVID-19 and the clinic improves with admission of immunomodulators, the myocardial damage is thought to be secondary to inflammatory mediators (13,14). In our case series, the increased myocardial enzyme level and myocardial dysfunction upon admission and those parameters being improved on the third day of IVIg and steroid treatment and completely back to normal by the time of discharge are coherent with the literature.

Table 5. Follow-up times and treatment of patients with MIS-C

Patient characteristic	All patients (n=16)
Clinical status, n (%)	
Mild	10 (62.5)
Moderate	4 (25)
Severe	2 (12.5)
Treatment, n (%)	
Glucocorticoid (methylprednisolone)	16 (100)
IVIg (2 gr/kg)	16 (100)
Acetylsalicylic acid (antiaggregant dose)	16 (100)
Enoxaparin	11 (68.75)
Inotrope treatment	3 (18.5)
Follow-up clinic, n (%)	
Pediatric intensive care unit	4 (25)
Pediatric unit	12 (75)
Inpatient follow-up days, median (range)	10 (7-17)

IVIg: IV immunoglobulin, MIS-C: Multisystem inflammatory syndrome in children

In contrary to other European studies, our morbidity was lower (4,6) and 18.5% required inotrope agents. Our patients did not require invasive mechanical ventilation support or mechanical circulation support. In our case series, the average left ventricle EF was 63.1%, which is higher than the 35 patient case series of Belhadjer et al. (6) (LV EF <30%). Inotropic agent usage (80%), mechanical ventilation support (62%), mechanical circulation support (28%), IVIg (71%) and corticosteroid treatment (34%) were higher in the other cohort studies, compared to our study. In our case series, the left ventricle function's improvement and healing rate was 100% (16/16) whereas Belhadjer et al. (6) reported their rate as 71%. Improvement of ventricular function was found to be in correlation with the normal levels of troponin-I and pro-BNP levels prior to discharge. It is thought that the high morbidity rate of other studies is due to the fact that they faced this syndrome before it was better understood.

In the study by Radia et al. (15), 68% of MIS-C cases required pediatric intensive care unit admission, whereas in our series, 25% of our patient were followed in the pediatric intensive care unit.

In the laboratory findings, CRP, procalcitonin and ferritin were found to be severely increased. Other commonly seen abnormal levels were hyponatremia, hypoalbuminemia, abnormal kidney function tests, high troponin and pro-BNP. In the complete blood count, lymphopenia, neutrophilia and thrombocytopenia were the most common abnormalities (4-6). Increased levels of CRP, procalcitonin, troponin and pro-BNP were found to be severely high upon admission, lower on the third day of treatment and back to normal upon discharge. The sodium and albumin levels were found to be low at the beginning of the treatment and were seen to be within the normal range by the time of discharge. Laboratory findings were helpful in the diagnosis of our patients.

In pediatric population, MIS-C has similarities to hyper-inflammatory syndromes such as KD, hemophagocytic lymphohistiocytosis, macrophage activation syndrome and toxic shock syndrome (16). This similarity is expected since all these syndromes, with different etiologies, are results of uncontrolled activation of inflammatory pathways. There are multiple non-specific inflammatory markers reported for MIS-C, none of which is sensitive or specific to this syndrome.

Treatment modalities, used in other hyper-inflammatory syndromes, are used in order to control the hyper-inflammatory seen in MIS-C. There is no proof reported for the immunomodulatory treatment strategies in the treatment of MIS-C. The long-term effects of cardiac involvement are unclear; however, it may be of the same importance as similar hyper-inflammatory diseases such as KD (17).

Conclusion

In our study, important clinical, biochemical and radiologic findings of the MIS-C cases that we followed in our clinic were identified and our clinical and pediatric cardiology approaches were evaluated. More of multi centered studies including more patients are required in order to identify the clinical characteristics, risk factor, immunomodulatory treatments and supportive treatment options including the anticoagulant agents.

Being similar to KD, since it also has cardiac involvement, early diagnosis and treatment of MIS-C are of outmost importance in order to observe the possible long-term complications of cardiac involvement.

Ethics

Ethics Committee Approval: Ethical approval was taken from the Ethical Board of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşçıoğlu Training and Research Hospital on 22/03/2021 with the registry number E-48670771-514.10.

Informed Consent: Medical consent forms were signed by the parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., M.E., Ö.B.G., Ü.K.B., S.H.O., Design: A.Ö., M.E., Ö.B.G., Ü.K.B., S.H.O., Data Collection or Processing: A.Ö., S.M.I., V.T., Analysis or Interpretation: A.Ö., M.E., S.H.O., Ö.B.G., Ü.K.B., Writing Draft: A.Ö., M.E., S.H.O., V.T., S.M.I., Final Approval and Responsibility: A.Ö., M.E., S.H.O., Ö.B.G., Ü.K.B., S.M.I., V.T.

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