Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2021.21162

The Comparison of Children Who Were Diagnosed with COVID-19 in the First and the Second Waves of the SARS-CoV-2 Pandemic

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What is already known on this topic?

- *COVID-19 is a clinical condition with pneumonia caused by SARS-CoV2.*
- *Although COVID-19 is more common in adults, it has been detected in children of all ages.*
- *There is very little data in the literature comparing the effects of the first and second waves on children.*

What this study adds on this topic?

- *This is the first national report which compares the epidemiological and clinical findings of the first and second waves of the pandemic in children.*
- *The present study has demonstrated that, in the second wave of the pandemic, COVID-19 disease affected older children more, there was less intra-familial contraction and the severity of disease was milder.*
- *Although the use of inappropriate drugs was abundant in the first wave, this decreased in the second wave due to better understanding of the disease.*

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Received: May 21, 2021
Accepted: August 12, 2021

ABSTRACT

Objective: To compare the clinical and laboratory findings and short-term outcomes of those children diagnosed with COVID-19 in the first and second waves of the SARS-CoV-2 pandemic.

Methods: A retrospective study was conducted at a suburban community hospital during a 1-year period. All children who were less than 18 years of age and confirmed with COVID-19 were included in the study population. The demographics, clinical features, laboratories, treatments given, hospitalizations, and outcomes were analyzed.

Results: A total of 198 patients were enrolled; median age was 9.3 years. One-hundred four patients were diagnosed with COVID-19 disease in the first wave and 94 (47.5%) patients were diagnosed in the second wave of the pandemic. Those patients who were diagnosed with COVID-19 in the first wave of the pandemic were significantly younger than those in the second wave (medians: 2.7 years vs. 15 years respectively, $P < .001$). Intra-familial contact was detected in 66.4% vs. 33.6% in the first and second waves of the pandemic, respectively ($P < .001$). Asymptomatic patients were higher in the second wave than in the first wave ($P < .001$). Additionally, moderate-to-critically ill patients were significantly higher in the first wave than in the second wave ($P < .001$). The rate of multisystem inflammatory syndrome (MIS-C) cases was 0.32% in this study.

Conclusion: In children, COVID-19 disease affected older children, there was less intra-familial contact and the severity of the disease was milder in the second wave of the pandemic in comparison to the first wave. MIS-C was encountered in the second wave of the pandemic.

Keywords: COVID-19, SARS-CoV2, children, MIS-C, pandemic

INTRODUCTION

In patients diagnosed with pneumonia in December 2019 in Wuhan, China, a new type of coronavirus was detected as the etiological agent and the manifestations of pneumonia caused by this type of coronavirus was named "severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)."[1] As a result of this new type of coronavirus spreading all over the world and affecting many countries, it was defined as "coronavirus-related disease-2019 (COVID-19)" by the World Health Organization (WHO) and accepted as a pandemic.[2,3] The first COVID-19 case in our country (Turkey) was seen on March 11, 2020, and more than 2.5 million cases had been reported nationwide as of February 2021.[4]

While the incidence of COVID-19 disease in children was reported to be 1-2% in the early reports from China, the United States of America and Italy, it was stated that this rate was

Cite this article as: Turan C, Basa EG, Elitez D, Yılmaz O, Gümüş E, Anıl M. The comparison of children who were diagnosed with COVID-19 in the first and the second waves of the SARS-CoV-2 pandemic. *Turk Arch Pediatr.* 2021; 56(6): 596-601.

1-8% worldwide in subsequent reports.[5-9] In the light of the information obtained from countries heavily affected by the SARS-CoV-2 pandemic, it has been observed that the effects of COVID-19 disease in children are different and milder than in adults, and it rarely causes severe and/or critical illness or death in children.[5,10,11] The effects, treatment modalities, outcomes, and mortality rates of the first and second wave of the COVID-19 pandemic on patients have been reported in several countries. Accordingly, in the second wave, it was observed that the age groups, the severity of disease and also treatment methods (drugs, invasive, and/or non-invasive ventilation) changed. In paediatric populations, there is very little data regarding differences in the symptoms, clinical findings, treatments, and prognoses between the first and the second waves of the pandemic.

In Turkey, the first wave of COVID-19 began in March 2020. Since the first case was seen, the Turkish government progressively increased social distance and mask measures. Preschools were closed between March 2020 and June 2020. In addition, primary schools, secondary schools, and universities were closed until 2021. A complete lockdown was implemented in May 2020 but life returned to relative normality with only social distancing and mask measures in July 2020. At the end of August 2020, the number of COVID-19 started to increase again. The Turkish government started to reimplement stricter measures such as banning closed area social activities, closing entertainment premises such as bars, and weekend and nighttime regional and national lockdowns as well as travel related measures were implemented.

The differences and/or similarities between the first and second waves in terms of clinical characteristics, laboratories, outcomes, and fatalities with regards to children are not well-known and no studies had been conducted on this issue in our country as of the time of this study.

In this study, we aimed to compare the clinical and laboratory findings of those children who were diagnosed with COVID-19 in the first and second waves of the disease. Secondly, we also aimed to investigate the differences between the treatments given and outcomes achieved for these children in the first and second waves.

METHODS

Study Design

This study was retrospectively conducted in Buca Seyfi Demirsoy Teaching and Research Hospital, Pediatric Emergency Department between March 11, 2020 and March 11, 2021. In this study, the SARS-CoV-2 pandemic from March 11, 2020 to August 31, 2020 was accepted as the "First Wave," and the period of the disease from September 1, 2020 to March 11, 2021 as the 'Second Wave" of the pandemic. Official approval to conduct this study was obtained from the Health Ministry and the Ethical Committee of Ege University (2020-05-20T12-55-46 and 20-7T/7). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Selection

All patients aged 0-18 years whose nasopharyngeal samples were obtained for polymerase chain reaction (PCR) test according to the COVID-19 disease guidelines for children published by the Ministry of Health of the Republic of Turkey were included in this study. Nasopharyngeal sampling indications were as follows: a patient (1) who had traveled within the previous 14 days to a location where there was community transmission of SARS-CoV-2; (2) who lived with someone who had traveled to a pandemic area within the previous 14 days; (3) whose relatives had been hospitalized for respiratory disease within the previous 14 days; or (4) whose relatives had been diagnosed with COVID-19 within the previous 14 days. Also, children who had fever and/or cough and/or respiratory distress were identified as suspected cases and tested. Patients with positive PCR test results, and those with negative PCR but positive anti-SARS-CoV-2 total antibodies were included in this study. Those patients whose medical records were missing were excluded from the study.

Definitions

Those patients diagnosed with COVID-19 were classified into 5 groups according to the severity of disease: (1) *Asymptomatic:* patients who test positive for SARS-CoV-2 by virologic testing using a PCR or total antibody test, but have no symptoms; (2) *Mild:* patients who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, and muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging; (3) *Moderate:* patients who have evidence of lower respiratory disease by clinical assessment or imaging and an oxygen saturation (SpO_2) ≥94%; (4) *Severe:* patients who have tachypnoea, SpO_2 <94% on room air at sea level, a ratio of the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltrates >50%; or (5) *Critically ill*: patients who have respiratory failure, septic shock, and/or multiple organ dysfunction.[12] Also, patients are diagnosed with multisystem inflammatory syndrome (MIS-C) if the following criteria are present: fever (>38.0°C) ≥24 hours, severe disease which requires hospitalization, evidence of inflammation in laboratory tests, multiple system involvement, no alternative diagnosis, and previous history evidence of SARS-CoV2 disease or a history of contact with a SARS-CoV2 positive person within the previous 4 weeks.

Data Collection and Assessment of Patients

The demographic data (gender and age) of those patients diagnosed with COVID-19 disease in the first and second waves of the SARS-CoV-2 pandemic, their complaints at admission and the severity of their disease were compared. In both pandemic waves, the oxygen and ventilation support [oxygen support (mask, high-flow nasal cannula (HFNC), Bilevel Positive Airway Pressure (BIPAP) or use of invasive mechanical ventilator)] received and the drug treatment preferences used according to national guidelines (hydroxychloroquine, oseltamivir, azithromycin, favipiravir, intravenous immunoglobulin (IVIG), and methylprednisolone) were evaluated.

The rates of hospitalization and paediatric intensive care unit (PICU) admittance and length of stay in the first and second waves and also the patients' short-term outcomes (morbidity, mortality) were compared. In addition, the treatments given and prognoses made of those patients who were diagnosed with MIS-C due to COVID-19 were analyzed.

Statistical Analysis

Data were analyzed using the program Statistical Package for the Social Sciences 25.0 (IBM, Armonk, NY: IBM Corp.). Continuous variables were expressed as mean ± standard deviation, median (interquartile range, IQR), and categorical variables as numbers (n) and percentages (%). When the parametric test assumptions were met, *t*-test was used to compare differences between independent groups. When parametric test assumptions were not met, Mann–Whitney *U*-test was used to compare differences between independent groups. The chi-squared or Fisher's exact probability tests were used to compare demographics. In all analyses, $P < .05$ was considered statistically significant.

RESULTS

Diagnoses

During this study period, 2479 patients who were admitted to a paediatric ED were examined. Among these patients, 225 patients in whom PCR tests were performed due to a suspicion of COVID-19 were included in this study. Six patients with missing medical records and 21 patients with negative PCR test results were excluded from the study (Figure 1). One-hundred four (52.5%) patients were diagnosed with COVID-19 in the first wave and 94 (47.5%) patients were diagnosed in the second wave of the pandemic (Figure 1). During the study period, the rate of COVID-19 positivity was found to be 7.9%. The distribution of diagnoses of COVID-19 during the study period are shown in Figure 2.

Demographic Data

The final analysis was performed for 198 patients; 56.1% (n = 111) were male. The male/female ratio was 1.3/1, and their median age was 9.3 years (minimum 4 days - maximum 18 years, IQR 1.4-15.6 years) (Table 1). Only 36 (18.2%) patients were younger than 12 months. Those patients who were diagnosed with COVID-19 in the first wave of the pandemic were significantly younger than those in the second wave (median, 2.7 years vs. 15 years, respectively) ($P < .001$) (Table 1). Also, 131 (66.2%) patients had a history of family contact. Intra-familial contact was detected in 87 (66.4%) and 44 (33.6%) patients in the first and second wave of the pandemic, respectively ($P < .001$).

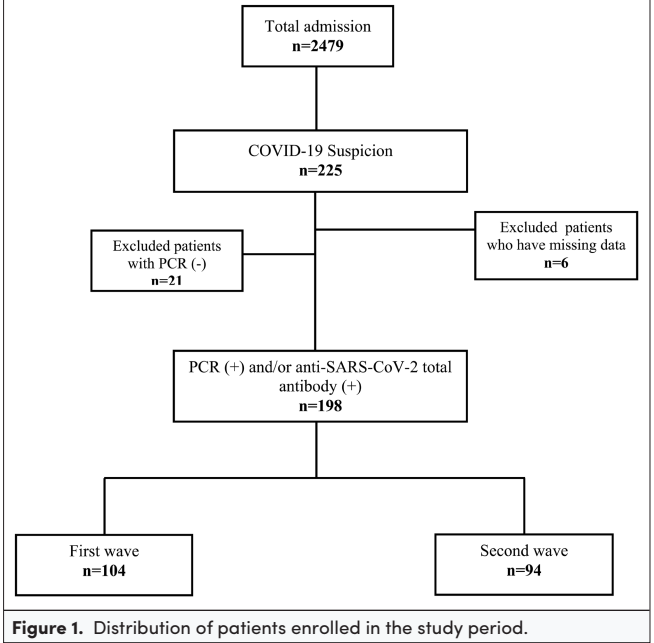

Figure 1. Distribution of patients enrolled in the study period.

Severity of Disease and Treatments

When the severity of the disease was evaluated, over half of patients (61.1%) had mild disease, 18.7% had moderate, 1.5% had severe, and only 1 patient had critical disease, while 18.2% of the patients were asymptomatic (Table 1).

However, the number of asymptomatic patients was higher in the second wave than in the first wave ($P < .001$). Additionally, moderate to critically ill patients were significantly higher in the first wave than in the second wave ($P < .001$) (Table 1). The treatment modalities used in both pandemic waves are shown in Table 2. The frequency of using combined azithromycin and oseltamivir or only hydroxychloroquine was significantly higher in the first wave than in the second wave ($P < .001$) (Table 2). In the first wave, while HFNC was applied to 8.7% of the patients, BIPAP to 1.9% and endotracheal intubation was applied to 1 patient; in the second wave of the pandemic, HFNC was applied to only 2 (2.0%) patients (Table 3). The use of invasive/non-invasive oxygen modalities was higher in the first wave than in the second wave (Table 3).

In the second wave of the pandemic, 8 patients were diagnosed with MIS-C (Table 4). Half of these patients were treated with IVIG. Methylprednisolone treatment was applied to the other half due to the lack of IVIG (Table 4). Additionally, acetylsalicylic acid (3-5 mg/kg/day) was used in all patients. No child death was observed due to COVID-19 or MIS-C in either period.

Outcomes

The outcomes and hospitalizations of the patients during the study period are shown in Table 3. Most patients (78.2%) were discharged from the ED. Twenty-eight (26.9%) patients were hospitalized in the first wave of the pandemic, and 6 (6.4%) patients in the second wave. In addition, 9 (8.6%) patients were admitted to the PICU in the first wave while no patient was admitted to the PICU in the second wave.

DISCUSSION

The current study is the first national report to compare the epidemiological and clinical findings of the first and second waves of the COVID-19 pandemic in children. The clinical severity of COVID-19 in the first wave was higher than in the second wave. However, MIS-C diagnosis emerged in the second wave. Other studies on this subject in the literature are extremely limited.

COVID-19, which emerged in the form of pneumonia due to SARS-CoV2 in December 2019, turned into a global epidemic in which more than 113 million people had been infected and more than 2.5 million people had died as of February 28, 2021.[13] Although COVID-19 is more common in the adult population, it has been detected in children of all ages.[11,12,14] In the literature, although the PCR positivity rates in children differ from country to country, it has been reported as 0.6% in Lithuania, 5% in France, 9% in Italy, and 11.2% in Spain.[15,16] In our study,

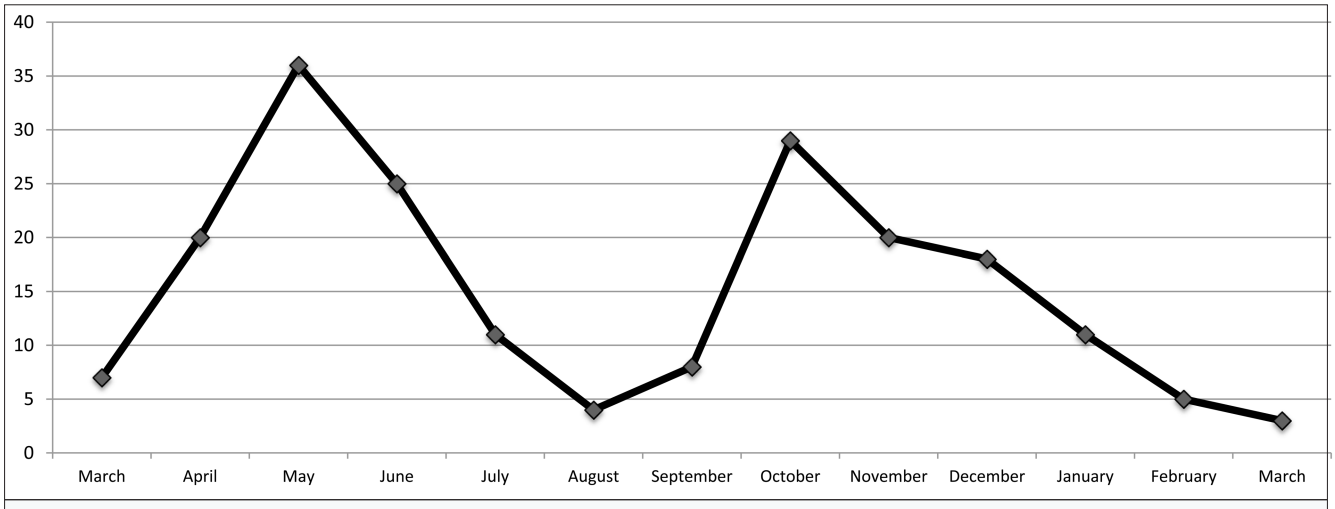

Figure 2. The first and second waves of COVID-19 pandemic and distribution of diagnoses by monthly during the study period.

Table 1. Epidemiologic and Clinical Characteristics of the Children Diagnosed as COVID-19 Disease During the First and Second Wave of the Pandemic, and Comparison of Treatment Methods

	Total (n = 198)	First Wave (n = 104)	Second Wave (n = 94)
Age (year) [median, (IQR)]	9.3 (1.4-15.6)	2.7 (0.9-10.0)	14.9 (10.9-16.9)*
Gender (n, M/F)	111/87	65/39	46/48
Intra-familial transmission (n, %)	131 (66.2)	87 (83.7)φ	44 (46.8)
Severity of disease (n, %)			
Mild	121 (61.1)	69 (66.3)	52 (55.3)
Moderate to critical	41 (20.7)	32 (30.8)	9 (9.6)
Moderate	37 (18.7)	28 (26.9)	9 (9.6)
Severe	3 (1.5)	3 (2.9)	0 (0)
Critical	1 (0.5)	1 (1.0)	0 (0)
Asymptomatic	36 (18.2)	3 (2.9)	33 (35.1)δ

F, female; M, male; IQR, interquartile range; IVIG, intravenous immunglobuline.
*Patients were significantly younger in the first wave than the second wave of the pandemic ($P < .001$) (Mann–Whitney *U*-Test); φIntra-familial contact was significantly higher in the first wave than the second wave ($P < .001$) (chi-square test); δAlthough the asymptomatic patients was more higher in the second wave than the first wave, moderate-to-critically ill patients were significantly higher in the first wave than second wave ($P < .001$ and $P < .001$) (Fisher's exact test).

the PCR positivity rate was 7.6%. The PCR positivity rate in our study was lower than in southern Europe. This was thought to be related to lifestyle, relationship contacts, and the closure of schools. Additionally, the fact that each country has different indications for taking PCR samples may lead to different PCR positivity rates by country.

The median age of the COVID-19 patients included in our study (7.2 years) was higher than in studies conducted in

Table 2. The Comparison of Treatment Methods in the First and Second Wave of the Pandemic

Treatment (n, %)	Total (n = 198)	First Wave (n = 104)	Second Wave (n = 94)
Azithromycin (1)	33 (16.7)	20 (19.2)	13 (13.8)
Oseltamivir (2)	7 (3.5)	2 (1.9)	5 (5.3)
Hydroxychloroquine (3)	5 (2.5)	4 (3.8)	1 (1.1)
Favipiravir (4)	8 (4.0)	0 (0)	8 (8.5)
IVIG (5)	4 (2.0)	0 (0)	4 (4.3)
Methylprednisolone (6)	4 (2.0)	0 (0)	4 (4.3)
1+2	65 (32.8)	65 (62.5)	0 (0)
1+3	2 (1.0)	2 (1.9)	0 (0)
1+2+3	1 (0.5)	1 (1.0)	0 (0)
3+4	0 (0)	0 (0)	0 (0)
None	69 (34.8)	10 (9.6)	59 (62.7)

F, female; M, male; IQR, interquartile range; IVIG, intravenous immunglobuline.

Table 3. Oxygen Treatments Modalities and Outcomes of the Children Diagnosed as COVID-19 Disease at the Pediatric ED During the First and Second Waves of the Pandemic

	First Wave	Second Wave
Oxygen treatment modalities, n (%)		
HFNC	9 (8.7)	2 (2.0)
CPAP/BIPAP	2 (1.9)	0 (0)
IMV	1 (1.0)	0 (0)
Hospitalization, n (%)		
Ward	28 (26.9)	6 (6.4)
PICU	9 (8.6)	0 (0)
Discharge	67 (64.4)	88 (93.6)

BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; PICU, pediatric intensive care unit; IMV, invasive mechanic ventilation; HFNC, high-flow nasal cannula oxygen therapy.

Table 4. Demographic and Laboratory Characteristics, Treatments, and Complications of the Patients Who Diagnosed With MIS-C

No.	Age (Year)	Gender	PCR	Anti-SARS-CoV-2 Total antibody	ECHO	Treatment	Complication
1	11	E	–	+	N	Metilprednizolon	No
2	8	E	–	+	N	IVIG	No
3	6.7	E	–	+	N	IVIG	No
4	1.3	E	–	+	N	Metilprednizolon	No
5	3.8	K	–	+	N	IVIG	No
6	1.5	K	–	+	N	Metilprednizolon	No
7	5.5	K	–	+	N	Metilprednizolon	No
8	5.8	E	–	+	N	IVIG	No

ECHO, echocardiography; F, female; IVIG, intravenous immunoglobulin; M, male; MIS-C, multisystem inflammatory syndrome; N, normal; PCR, polymerase chain reaction.

Italy (3.3 years) and in the United Kingdom (4.6), but similar to one conducted in China (6-7 years) and lower when compared to one conducted in the United States of America (USA) (11 years).[7,17-21] In the only paediatric study in the literature conducted by Krajcar et al.,[17] a fewer number of infants under 1 year of age had COVID-19 in the second wave of the pandemic, and COVID-19 was found more frequently in adolescents. In our study, the average age of children diagnosed with COVID-19 in the paediatric ED was significantly higher in the second wave than in the first wave. During the first and second waves, primary schools, secondary schools, and universities were generally closed and only pre-schools were open. For this reason, it was not thought that there was any difference in school-age children in the first and second waves of the pandemic. Based on our clinical experience, this finding may be related to the parents' preference of monitoring their small children at home, but admission to hospital for their older children.

At the onset of the pandemic, the most common cause of COVID-19 in children was reported to be in contact with other family members.[18,22] Krajcar et al.[17] found that the rate of intra-familial contact was lower in the second wave of the pandemic. Similar results were obtained in our study and children had less intra-familial contact during the second wave. The opening of schools after the first wave of the pandemic, less adherence to isolation measures, and increased contact of children with other people as a result of geographical and seasonal changes may explain these results.

In studies conducted in many European countries, and also Iran, South Korea, and the USA, it has been reported that asymptomatic children are in the range of 4-28%.[14,17,23-26] Similar to the literature, 16.4% of patients in our study were asymptomatic. Krajcar et al.[17] reported that drug use in children was at a higher rate in the first wave of the pandemic. Similar to Krajcar et al.,[17] due to the higher number of asymptomatic patients but lower number of severely ill patients, drug therapy was used less frequently in the second wave of the pandemic. Parallel to this finding, medical treatment, oxygen support, and hospitalization in COVID positive paediatric patients were less often used in the second wave compared to the first wave. The experience of physicians after the first wave of the pandemic, better recognition of the disease, better knowledge of the approach to and management of the disease, and the implementation of isolation rules can explain these lower rates in the second wave.

MIS-C cases were first reported in children in April 2020, and its incidence has been reported to be 0.14%.[27,28] In the literature, IVIG treatment is recommended primarily and frequently according to the severity of the disease in MIS-C cases; methylprednisolone treatment is used as an alternative treatment.[29-31] In our study, rates of MIS-C cases were higher (0.32%) when compared to the literature. This situation can be explained as follows; information on MIS-C disease is increasing day by day and physicians are aware of this disease. Although IVIG was preferred as the first choice in treatment, methylprednisolone was used in 50% of the patients due to the cost and difficulty in availability of IVIG. Clinical response was obtained in all patients, and no treatment-related complications developed.

Our study has some limitations. First, the retrospective design of our study is the most crucial limitation. Secondly, it reflects the experience of a single center. Despite its limitations, this report is one of the pioneering studies comparing pediatric cases diagnosed with COVID-19 in 2 periods of the SARS-CoV-2 pandemic in the world.

CONCLUSION

In conclusion, compared to the first wave of the pandemic, those children diagnosed with COVID-19 in the second wave were older, the rate of intra-familial contact was lower, and the clinical severity of the disease was milder. MIS-C was encountered in the second wave of the pandemic. We believe that the most important result of this study is that the characteristics of the disease are better known day by day and also that the continuous new publications and updated and more effective approaches have been effective on the results.

Ethical Committee Approval: Official approval to conduct this study was obtained from the Health Ministry and the Ethics Committee of Ege University (2020-05-20T12-55-46 and 20-7T/7).

Informed Consent: Informed consent was not obtained due to the retrospective design of this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – C.T., E.G.B., M.A.; Design – C.T., D. E., M.A.; Supervision – C.T. M.A.; Materials – C.T., E.G.B., D.E., E.G., O.Y.; Data Collection and/or Processing – C.T., E.G.B., D.E., E.G., O.Y.;

Analysis and/or Interpretation – C.T., E.G.B., M.A.; Literature Review – C.T., M.A.; Writing – C.T., E.G.B., M.A.; Critical Review – C.T., M.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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