Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

American Journal of Emergency Medicine 48 (2021) 307–311

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Predictive value of cardiac markers in the prognosis of COVID-19 in children

Ufuk Utku Güllü [a], Şükrü Güngör [b], Sevcan İpek, MD [c,*], Sadık Yurttutan [d], Cengiz Dilber [e]

[a] Department of Pediatrics, Division of Pediatric Cardiology, Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Kahramanmaraş, Turkey
[b] Department of Pediatrics, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Kahramanmaraş, Turkey
[c] Department of Pediatrics, Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Kahramanmaraş, Turkey
[d] Department of Pediatrics, Division of Neonatal Intensive Care Unit, Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Kahramanmaraş, Turkey
[e] Department of Pediatrics, Division of Pediatric Neurology Kahramanmaras Sutcu Imam University, Faculty of Medicine, Kahramanmaraş, Turkey

ARTICLE INFO

Article history:
Received 23 April 2021
Received in revised form 6 June 2021
Accepted 28 June 2021

Keywords:
Cardiac
COVID-19
Children
proBNP
SARS-CoV-2
Troponin I

ABSTRACT

Background and aim: Occasionally, children with COVID-19 may develop arrhythmia, myocarditis, and cardiogenic shock involving multisystemic inflammatory syndrome in children (MIS-C). This study aimed to identify the laboratory parameters that may predict early cardiovascular involvement in these patients.
Materials and methods: Data of 320 pediatric patients, aged 0–18 years (average age, 10.46 ± 5.77 years; 156 female), with positive COVID-19 reverse transcription–polymerase chain reaction test and with cardiac biomarkers at the time of admission to the pediatric emergency department were retrospectively scanned. The age, sex, COVID-19-associated symptoms, pro-brain natriuretic peptide (proBNP), CK-MB, and troponin I levels of the patients were recorded.
Results: Fever was noted in 58.1% of the patients, cough in 29.7%, diarrhea in 7.8%, headache in 14.7%, sore throat in 17.8%, weakness in 17.8%, abdominal pain in 5%, loss of taste in 4.1%, loss of smell in 5.3%, nausea in 3.4%, vomiting in 3.8%, nasal discharge in 4.4%, muscle pain in 5%, and loss of appetite in 3.1%. The proBNP value ≥282 ng/L predicted the development of MIS-C with 100% sensitivity and 93% specificity [AUC: 0.985 (0.959–1), $P < 0.001$]; CK-MB value ≥2.95 with 80% sensitivity and 77.6% specificity [AUC: 0.792 (0.581–1), $P = 0.026$]; and troponin I value ≥0.03 with 60% sensitivity and 99.2% specificity [AUC: 0.794 (0.524–1)].
Conclusions: Cardiac markers (proBNP and troponin I), especially proBNP, could be used to detect early diagnosis of cardiac involvement and/or MIS-C in pediatric patients with COVID-19 and to predict related morbidity and mortality.

© 2021 Elsevier Inc. All rights reserved.

1. Introduction

After the first cases were reported in Wuhan in December 2019, the World Health Organization (WHO) declared the SARS-CoV-2 (COVID-19) outbreak a pandemic on March 11, 2020 [[1]]. Initially, it was thought that the infection, which caused very high mortality and morbidity among adults, people with comorbid conditions, and those with advanced age, did not cause a significant health problem in children. However, a case series of eight previously healthy children presenting with fever, hyper inflammation, and cardiovascular shock was reported in late April 2020 [2]. It was understood that this condition, which is thought to be a disease similar to Kawasaki disease, was different from Kawasaki in terms of presentation and age group as the number of cases increased. While Kawasaki disease was diagnosed mostly with mucocutaneous findings, conditions such as gastrointestinal problems, severe left ventricular systolic dysfunction, and vasoactive and vasopressor need were seen to be more prominent in multisystem inflammatory syndrome in children (MIS-C) [3]. As the pandemic progressed, the Centers for Disease Control and Prevention published the MIS-C diagnostic criteria in children, as the number of patients diagnosed with MIS-C increased in proportion to the increase in the number of pediatric patients related to it [4]. According to these diagnostic criteria, for the diagnosis of MIS-C; being under the age of 21, fever exceeding 38 degrees for 24 h, laboratory data showing inflammation (C-reactive protein, erythrocyte sedimentation rate, fibrinogen, D-Dimer, ferritine, LDH, IL6, neutrophilia and hypoalbuminemia), serious illness to be hospitalized, 2 and more organ involvement (cardiac, renal, respiratory, hematologic, gastrointerstinal, dermatologic and neurologic), no other plausible diagnosis, SARS-CoV2 infection or exposure defined as positive PCR, serology or antigen test and COVID-19 exposure within four weeks prior to onset conditions must be met.

* Corresponding author at: Department of Pediatrics, Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Avşar Kampüsü, Kahramanmaraş 46100, Turkey.
E-mail address: sevcanipek@ksu.edu.tr (S. İpek).

https://doi.org/10.1016/j.ajem.2021.06.075
0735-6757/© 2021 Elsevier Inc. All rights reserved.

The increasing importance of cardiac markers such as pro-BNP, troponin, CK-MB and creatine kinase in the follow-up of cases led to their use in diagnosing the disease and in the follow-up of treatment processes [2,5,6].

This study aimed to retrospectively examine the files of patients who were admitted to the pediatric emergency department with a positive COVID-19 reverse transcription–polymerase chain reaction (RT-PCR) test, and to investigate laboratory markers that could predict cardiovascular involvement.

2. Materials and methods

2.1. Study design

In this retrospective, single-center, observational study, pediatric patients aged 0–18 years with a positive COVID-19 RT-PCR test and with cardiac markers at admission to the pediatric emergency were included between April 1, 2020, and December 1, 2020. ProBNP, troponin I, creatine kinase and CK-MB were screened as cardiac markers.

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from local ethics committee before the study (2021/06–03).

2.2. Exclusion criteria

Patients with a negative COVID-19 RT-PCR test at admission but subsequently found positive were not included in the study. Patients without cardiac markers were excluded.

2.3. Data analysis

The demographic characteristics and clinical and laboratory findings (hemogram, pro–brain natriuretic peptide (proBNP), creatine kinase, CK-MB, and troponin I) were scanned from medical records of the patients included in the study.

2.4. COVID-19 RT-PCR analysis

Nasopharyngeal swabs of the patients were examined using the BIO-RAD CFX96 Real-Time System C1000 Touch Thermal Cycler Device, SARS-CoV-2 Double Gene RT-qPCR 1000 Rxn kit, and COVID-19 RT-PCR kit.

2.5. Statistical analyses

Statistical Package for the Social Sciences for Windows 22 software was used for statistical analysis. Study variables were presented as number (n) – percentage (%) and mean ± standard deviation. The normal distribution of variables was tested using the Kolmogorov–Smirnov test. Normally distributed parameters were evaluated by one-way analysis of variance or Student t-test; the Kruskal–Wallis or Mann–Whitney U test was used for numerical variables that did not show normal distribution. Student t-test, Mann–Whitney U test, and chi-square test were used to evaluate statistical significance. The receiver operator characteristic (ROC) curve analysis was performed to find an optimal cut-off point for the MIS-C prediction. A P value less than 0.05 was considered statistically significant.

3. Results

A total of 3249 pediatric patients that had fever and/or COVID-19 contact applied to the COVID-19 pediatric emergency service on the specified dates, and 536 of them tested positive for COVID-19 using the RT-PCR test. Of these patients, 320 children in whom cardiac markers were screened were included in the study. The average age of the patients was 10.46 ± 5.77 years (0–18); 156 (48.8%) were female and 164 (51.2%) male. While 51 of the patients (15.9%) had no history of contact, 269 (84.1%) had a history of contact. When the patients were evaluated according to their presenting symptoms, fever was noted in 186 (58.1%) patients, cough in 95 (29.7%) patients, diarrhea in 25 (7.8%) patients, headache in 47 (14.7%) patients, sore throat in 57 (17.8%) patients, nasal discharge in 14 (4.4%) patients, nausea in 11 (3.4%) patients, vomiting in 12 (3.8%) patients, abdominal pain in 16 (5%) patients, fatigue in 57 (17.8%) patients, loss of taste in 13 (4.1%) patients, loss of smell in 17 (5.3%), myalgia in 16 (5%) patients, and loss of appetite in 10 (3.1%) patients. Moreover, 290 of 320 patients were symptomatic; 30 (9.4%) patients had no complaints. The duration of the complaints was 2 ± 2.20 (1–14) days on average. Further, 213 of the patients (66.6%) were followed up in outpatient, 102 (31.9%) were admitted to the pediatric emergency service, and 5 (1.5%) were admitted to the intensive care unit (Table 1).

The average values of laboratory parameters of the patients with COVID-19 infection were as follows: white blood cell count (WBC) (10^9): 6.821 ± 2.784 (min:2.21– max:25.12), hemoglobin (Hb) (g/dL): 13.15 ± 1.60 (min:7.9–max:17.4), platelet (10^9 L): 254.72 ± 74.01 (min:81– max:592), C-reactive protein (CRP) (mg/L): 5.82 ± 8.56 (min:3–max:62), procalcitonin (μg/L): 0.086 ± 0.125 (min:0.02–max:1.69), proBNP (ng/L): 248.09 ± 1699.40 (min:35–max:28,000), creatinine kinase (CK) (U/L): 110.47 ± 78.89 (min:32-max:814), CK-MB (μg/L): 2.97 ± 2.45 (min:0.5–max:19), and troponin I (μg/L): 0.003 ± 0.20 (min:0–max:0.23) (Table 2).

The patients diagnosed with MIS-C were as follows: An 11-year-old male with severe sequelae was followed up with cerebral palsy and epilepsy. He was also operated on from aortic coarctation. He was admitted to the emergency department with fever, diarrhea, vomiting, and cough. He had pneumonia. Ferritin was 127 μg/L, procalcitonin 0.57 μg/L, and neutrophil $22.560{\cdot}10^9$/L. There was a period of 1 week between the onset of complaints and the time of admission to the emergency department, and when the patient came to the emergency department, he was diagnosed with MIS-C according to the CDC diagnostic criteria since he had multi-system involvement. The other patient, a 1-month-old girl, was being followed up with aortic coarctation. The time elapsed between the patient's admission to us and the detection of COVID-19 PCR positive in another hospital was 4 days. When the patient applied to us, he had complaints of fever and decreased feeding. Ferritin was 371 μg/L, procalcitonin 0.1 μg/L, proBNP 28,000 ng/L,

Table 1
Demographic characteristics of pediatric patients with COVID-19 infection.

	Mean ± SD (min–max)
Age (year)	10.46 ± 5.77 (0–18)
	N (%)
Gender Female	156 (48.8)
Male	164 (51.2)
Have symptoms	290 (90.6)
No symptoms	30 (9.4)
Fever	186 (58.1)
Cough	95 (29.7)
Diarrhea	25 (7.8)
Headache	47 (14.7)
Throat ache	57 (17.8)
Runny nose	14 (4.4)
Nausea	11 (3.4)
Vomiting	12 (3.8)
Abdominal pain	16 (5)
Weakness	57 (17.8)
Loss of taste	13 (4.1)
Loss of smell	17 (5.3)
Myalgia	16 (5)
Loss of appetite	10 (3.1)
Ambulatory	213 (66.6)
Follow-up at the pediatric emergency service	102 (31.9)
Follow-up in intensive care	5 (1.5)

Statistics: Descriptive statistics and frequency.

Table 2
Evaluation of mean laboratory values of patients with COVID-19 infection.

	Mean ± SD	Minimum–Maximum
WBC (10^9 L)	6.821 ± 2.784	2.21–25.12
Hb (g/dL)	13.15 ± 1.60	7.9–17.4
PLT (10^9 L)	254.72 ± 74.01	81–592
CRP (mg/L)	5.82 ± 8.56	3–62
Procalcitonin (μg/L)	0.086 ± 0.125	0.02–1.69
ProBNP (ng/L)	248.09 ± 1699.40	35–28,000
CK (U/L)	110.47 ± 78.89	32–814
CK-MB (μg/L)	2.97 ± 2.45	0.5–19
Troponin I (μg/L)	0.003 ± 0.20	0–0.23

Statistics: Descriptive. Abbreviations: CK, Creatine kinase; CRP, C-reactive protein; Hb, hemoglobin; MIS-C, multisystem inflammatory syndrome in children; proBNP, pro–brain natriuretic peptide; WBC, white blood cell count.

troponin I 0.17 μg/L. This patient was diagnosed as MIS-C when he applied to the emergency department according to the CDC diagnostic criteria. 0ur other patient who developed MIS-C was a 14-year-old girl with hypertrophic cardiomyopathy, mitral valve regurgitation, and with ICD (Implantable cardioverter defibrillator). She presented with fever, cough and headache. The complaints of this patient started 2 weeks before he applied to us. Lymphocyte was $0.970{\cdot}10^9$/L, troponin I 0.23 μg/L, proBNP 7940 ng/L, procalcitonin 0.08 μg/L. This patient was diagnosed according to the CDC criteria. The other patient was a 3-month-old male patient. He presented with fever, diarrhea and lack of urine. He was followed with ventricular septal defect and pulmonary hypertension. The patient had severe dehydration at the time of admission. Creatinine was 5.76 mg/dL, procalcitonin 0.48 μg/L, ferritin 158 μg/L. The COVID-19 PCR of this patient resulted on the 3rd day of hospitalization and was diagnosed as MIS-C. The other MIS-C patient was 6 days old. He applied with fever, vomiting, decreased feeding and respiratory distress for 2 days. It was learned that his aunt and grandfather were diagnosed with COVID-19 and they loved and cared for the baby. The mother was COVID-19 PCR negative. Ferritin 273 μg/L, pro BNP 4440 ng/L, procalcitonin 0.16 μg/L. At the time of admission, the patient was defined as MIS-C according to the CDC criteria. There was no congenital cardiac anomaly in the echocardiography of the baby.

When the laboratory findings of COVID-19 patients with and without MIS-C were evaluated, no significant differences in WBC, Hb, PLT, CRP, and CK values ($P = 0.143$, 0.905, 0.343, 0.312, and 0.218, respectively) were found between the two groups. The procalcitonin, proBNP, CK-MB, and troponin I values were significantly higher in the group with MIS-C ($P = 0.004$, <0.001, 0.013, and < 0.001, respectively) (Table 3). The cut-off points of the laboratory parameters were determined using the ROC curve analysis to predict the development of MIS-C in patients with COVID-19. According to this analysis,

Table 3
Comparison of the laboratory findings of patients infected with COVID-19 with and without MIS-C.

	MIS-C (−) (315) Mean ± SD	MIS-C (+) (5) Mean ± SD	*P*
WBC (10^9 L)	6.75 ± 2.58	11.18 ± 8.27	0.143
Hb (g/dL)	13.14 ± 1.59	13.22 ± 2.24	0.905
PLT (10^9 L)	254.09 ± 73.62	294.40 ± 96.71	0.343
CRP (mg/L)	5.85 ± 8.62	4.00 ± 1.92	0.312
Procalcitonin (μg/L)	0.082 ± 0.120	0.278 ± 0.229	0.004
ProBNP (ng/L)	108.65 ± 231.56	8558.60 ± 11,237.50	<0.001
CK (U/L)	108.52 ± 74.62	231.80 ± 199.65	0.218
CK-MB (μg/L)	2.84 ± 2.11	7.56 ± 7.11	0.013
Troponin I (μg/L)	0.0012 ± 0.0104	0.0880 ± 0.1056	<0.001

Statistics: Mann–Whitney *U* test. Abbreviations: CK, Creatine kinase; CRP, C-reactive protein; Hb, hemoglobin; MIS-C, multisystem inflammatory syndrome in children; proBNP, pro–brain natriuretic peptide; WBC, white blood cell count.

Table 4
Determination of cut-off points of laboratory data that can predict MIS-C development.

	Cut-off value	AUC	Sensitivity	Specificity	Asymptotic 95% confidence interval	*P*
ProBNP	≥282	0.985	1	0.930	0.959–1	<0.001
CK-MB	≥2.95	0.792	0.800	0.776	0.581–1	0.026
Troponin I	≥0.03	0.794	0.600	0.992	0.524–1	0.024

Statistics: ROC curve analysis. Abbreviations: CK, Creatine kinase; MIS-C, multisystem inflammatory syndrome in children; proBNP, pro–brain natriuretic peptide.

proBNP ≥282 ng/L predicted the development of MIS-C with 100% sensitivity and 93% specificity [AUC: 0.985 (0.959–1), $P < 0.001$] in patients with COVID-19 infection. Moreover, CK-MB ≥2.95 μg/L could predict the development of MIS-C with 80% sensitivity and 77.6% specificity [AUC: 0.792 (0.581–1), $P = 0.026$]; and troponin $I = 0.03$ could do so with 60% sensitivity and 99.2% specificity [AUC: 0.794 (0.524–1), $P = 0.024$] (Table 4).

4. Discussion

COVID-19 disease is an infectious disease that affects the whole world, has devastating results in adult patients, and has a milder course in pediatric patients, but can result in severe consequences in pediatric patients who develop MIS-C [3]. According to a systematic review of 131 studies involving 7780 pediatric patients with COVID-19 infection from 26 countries, the most common clinical symptoms reported were rhinorrhea (20.0%), fever (59.1%), myalgia/fatigue (18.7%), and cough (55.9%) [7]. Fever (40%–80%), cough (50%–80%), and shortness of breath (13%–30%) were also reported in the pediatric case series [8-13]. In this study, fever was found in 58.1% of patients, cough in 29.7%, diarrhea in 7.8%, headache in 14.7%, sore throat in 17.8%, weakness in 17.8%, abdominal pain in 5%, loss of taste in 4.1%, loss of smell in 5.3%, nausea in 3.4%, vomiting in 3.8%, nasal discharge in 4.4%, muscle pain in 5%, loss of appetite in 3.1%, runny nose in 4%, myalgia in 5%, and anorexia in 3.1%. Moreover, 30 patients (9.4%) had no complaints, who presented only because of a history of contact. COVID-19 infection in young infants usually presents clinically with unexplained fever and mild respiratory symptoms [14], and acute respiratory distress syndrome develops rarely compared with adults [7]. The rate of hospitalization has been 10%–33% in adult patients with COVID-19 infection and 5.7%–20% in the pediatric population under 18 years of age. In addition, the intensive care unit admission rate has been 1.4%–4.5% in adults and 0.58%–2% in the pediatric population [15]. In a study conducted in pediatric patients with COVID-19 infection, severe cases were detected in 11% of infants and 3% in adolescents aged 16 years and more, and infants had more severe infections than older children [9]. Patients with comorbid disease and/or those younger than 1 year of age had a higher rate of severe infection [14]. In this study, in line with the literature, 213 patients (66.6%) were followed up as outpatients, 102 patients (31.9%) were admitted in the ward, and 5 patients (1.5%) were admitted in intensive care. Further, 80% of the patients were admitted to the pediatric intensive care unit (PICU) who had at least one comorbid condition (congenital heart disease, cerebral palsy, and epilepsy). In addition, 60% of the patients admitted to the PICU were less than 1-year old.

Of our MIS-C patients, 1 had acquired heart disease and 3 had congenital heart disease. The proBNP levels were higher in patients with heart disease compared with the healthy population [16]. However, on examining the published studies on this topic, the proBNP levels were generally lower than 1000 ng/L in patients with heart failure with left-to-right shunt [16-18]. In this study, although 80% of the patients diagnosed with MIS-C had heart disease, the mean value for proBNP was approximately eight times higher (8500 ng/dL) than that reported in previous studies. This difference might be because of the primary cardiac damage due to COVID-19-related MIS-C.

Natriuretic peptides are protein molecules released from the ventricles in response to volume or pressure load [19]. Brain natriuretic peptide (BNP) is synthesized and released mainly in left ventricular myocytes in response to ventricular volume expansion or stretching due to pressure loading of myocytes [20]. Initially, the hormone is synthesized as pre-pro BNP and then cleaved to proBNP. ProBNP also dissociates into active BNP and inactive NT-proBNP. BNP is a biologically active molecule that corrects myocardial dilation by causing natriuresis, vasodilation, and diuresis [21]. In a study using adult patients, the elevation of NT-proBNP was suggested to be an independent risk factor for in-hospital deaths among patients with severe COVID-19 [22]. In this study, the high rate of proBNP in all patients admitted to the PICU compared with other patients revealed its prognostic importance following the literature.

Typical symptoms of MIS-C are fever, rash, abdominal pain, diarrhea, and vomiting. Low blood pressure, shock, and heart abnormalities are common physical symptoms. Often, laboratory results show high neutrophil count, high CRP, low lymphocyte count, and abnormal blood results suggestive of severe inflammation [23]. COVID-19 infection triggers macrophage activation and helper-T-cell activation in its follow-up. It leads to B-cell and plasma-cell activation, massive cytokine release, and antibody production. Immune dysregulation and hyperactive immune response develop [3,24]. Valverde et al. reported that cardiac involvement was common in 286 children with MIS-C in Europe, with significantly higher levels of NT-pro-BNP, ferritin, D-dimer, and cardiac troponin in addition to high levels of CRP and procalcitonin [25]. In the patient group included in the present study, MIS-C was detected in five (1.5%) patients. In accordance with the literature, higher proBNP, CK-MB, troponin I, and procalcitonin values were found at the time of first application to the pediatric emergency service of children with COVID-19 infection in patients with MIS-C than those without. Unlike in the literature, a proBNP value of 282 in this study was predictive for the development of MIS-C with 100% sensitivity and 93% specificity. Similarly, CK-MB ≥2.95 and troponin $I \geq 0.03$ had predictive values for MIS-C (Table 4). The present study was novel in predicting the development of MIS-C in pediatric patients found positive for COVID-19 using RT-PCR test who were admitted to the emergency department.

In our country, everyone can apply the emergency departments. Every patient who admitted to the emergency department is evaluated. Patients are taken to red, yellow, and green areas, depending on their urgency. Accordingly, outpatient patients who are admitted in the green area, who are stable in terms of their general condition and who can be treated on an outpatient basis, patients with simple health problems such as all kinds of pain with no high risk and low-risk illness without active complaints are evaluated. In the yellow and red areas, more risky and critical patients are evaluated [26,27]. Thus, there were patients in the green field among the patients who were evaluated in the pediatric emergency department in the study. Therefore, since our study includes low-risk patients, the cut-off values found may be valuable to clinicians in demonstrating the severity of the disease in laboratory.

This study had some limitations. It was retrospective in nature, small number of patients were included in the study, and a small number of patients were in the MIS-C group. However, this study is valuable being the first to indicate a cut-off in the values of laboratory parameters in predicting patients with MIS-C.

5. Conclusions

In conclusion, early detection of cardiac involvement and/or MIS-C, one of the most important prognostic factors in COVID-19 infection, is vital. Since the study includes low-risk patients, the cut-off values stated are important in predicting the prognosis of the patients. This study provides data that will assist clinicians in identifying cardiac involvement and/or MIS-C with poor prognosis in pediatric patients with COVID-19 infection. In addition, this study will shed light on the larger and more comprehensive studies required to determine the prognostic factors of COVID-19 infection.

Funding

None.

Ethical approval

This study was approved by the ethics committee of the Kahramanmaras Sutcu *Imam* University before the study (2021/06–03).

Author contribution statement

U. U. G conceived, designed the study and collected the data; S.İ, Ş. G, S. Y, and C. D collected data and interpreted the data; S.İ, UUG, and Ş. G analyzed, discussed and interpreted the data. S. İ and U. U. G composed the first draft of the manuscript. All authors approved the final version of the manuscript for submission.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

[1] Ghebreyesus TA. WHO director-general's opening remarks at the media briefing on COVID-19-11 March 2020. World Health Organization; 2020.
[2] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet (London, England). 2020;395(10237):1607–8. https://doi.org/10.1016/s0140-6736(20)31094-1.
[3] Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel, Switzerland). 2020;7(7). https://doi.org/10.3390/children7070069.
[4] CDC. Multisystem inflammatory syndrome in children (MIS-C). Centers for Disease Control and Prevention; (February 11, 2020.
[5] Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142(5):429–36. https://doi.org/10.1161/circulationaha.120.048360.
[6] Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet (London, England). 2020;395(10239):1771–8. https://doi.org/10.1016/s0140-6736(20)31103-x.
[7] Feld L, Belfer J, Kabra R, Goenka P, Rai S, Moriarty S, et al. A case series of the 2019 novel coronavirus (SARS-CoV-2) in 3 febrile infants in New York. Pediatrics. 2020;146(1). https://doi.org/10.1542/peds.2020-1056.
[8] Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: a systematic review. EClinicalMedicine. 2020;24:100433. https://doi.org/10.1016/j.eclinm.2020.100433.
[9] Jiehao C, Jin X, Daojiong L, Zhi Y, Lei X, Zhenghai Q, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. 2020;71(6):1547–51. https://doi.org/10.1093/cid/ciaa198.
[10] Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta paediatrica (Oslo, Norway: 1992). 2020;109(6):1088–95. https://doi.org/10.1111/apa.15270.
[11] Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of Covid-19 in children in early January 2020 in Wuhan, China. N Engl J Med. 2020;382(14):1370–1. https://doi.org/10.1056/NEJMc2003717.
[12] Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020;26(4):502–5. https://doi.org/10.1038/s41591-020-0817-4.
[13] Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy. N Engl J Med. 2020;383(2):187–90. https://doi.org/10.1056/NEJMc2007617.
[14] Stephanie Bialek RG, Hughes Michelle, McNamara Lucy A, Pilishvili Tamara, Skoff Tami. Coronavirus Disease 2019 in children - United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422–6. https://doi.org/10.15585/mmwr.mm6914e4.
[15] Shen KL, Yang YH. Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. World J Pediatr. 2020;16(3):219–21. https://doi.org/10.1007/s12519-020-00344-6.
[16] Isah IA, Sadoh WE, Iduoriyekemwen NJ. Usefulness of amino terminal pro-B-type natriuretic peptide in evaluating children with cardiac failure. Cardiovasc Diagn Ther. 2017;7(4):380.

[17] Ekure EN, Okoromah CA, Ajuluchukwu JN, Mbakwem A, Oladipo OO. Diagnostic usefulness of N-terminal pro-brain natriuretic peptide among children with heart failure in a tertiary hospital in Lagos, Nigeria. West Afr J Med. 2011;30(1):29–34. https://doi.org/10.4314/wajm.v30i1.69881.

[18] Nevo I, Erlichman M, Algur N, Nir A. N-terminal pro B-type natriuretic peptide levels in infants and children with acute non-cardiac diseases. IMAJ. 2011;13(7):420–4.

[19] Maalouf R, Bailey S. A review on B-type natriuretic peptide monitoring: assays and biosensors. Heart Fail Rev. 2016;21(5):567–78. https://doi.org/10.1007/s10741-016-9544-9.

[20] Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi Jr JL. Biology of the natriuretic peptides. Am J Cardiol. 2008;101(3a):3–8. https://doi.org/10.1016/j.amjcard.2007.11.012.

[21] Cataliotti A, Boerrigter G, Costello-Boerrigter LC, Schirger JA, Tsuruda T, Heublein DM, et al. Brain natriuretic peptide enhances renal actions of furosemide and suppresses furosemide-induced aldosterone activation in experimental heart failure. Circulation. 2004;109(13):1680–5. https://doi.org/10.1161/01.Cir.0000124064.00494.21.

[22] Gao L, Jiang D, Wen XS, Cheng XC, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res. 2020;21(1):83. https://doi.org/10.1186/s12931-020-01352-w.

[23] Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine. 2020;26:100527. https://doi.org/10.1016/j.eclinm.2020.100527.

[24] Yurttutan S, Gullu UU, Ipek S. Anakinra after treatment with corticosteroids alone or with tocilizumab in patients with severe COVID-19 pneumonia and moderate hyperinflammation. Intern Emerg Med. 2021:1–3. https://doi.org/10.1007/s11739-021-02663-6.

[25] Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation. 2021;143(1):21–32. https://doi.org/10.1161/circulationaha.120.050065.

[26] KSU. Acil Servis İşleyiş Prosedürü. Kahramanmaraş Sütçü İmam Univesity, Health Practice and Research Hospital; 2016.

[27] Altindiş S, Ünal Ö. Acil Servis Kalite Standartlarında Türkiye'nin Durumu. J Biotechnol Strateg Health Res. 2017;1(2):51–9.