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ORIGINAL ARTICLE

The evaluation of the burden of multisystem inflammatory syndrome in children on health economics

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ABSTRACT

Objectives: This study aimed to evaluate the diagnostic tests and treatments applied in patients with multisystem inflammatory syndrome in children (MIS-C) and to determine the effect of the disease on health costs.

Patients and methods: This retrospective cohort study included 59 MIS-C patients (40 males, 19 females; mean age: 7.7±4.2 years; range, 4 months to 16.5 years) who were admitted and treated between April 1, 2020, and November 1, 2021. Demographic and clinical features with hospital costs and length of stay were retrospectively reviewed from the medical files and computerized system of the hospital. Direct medical care costs of items were calculated with the hospital perspective using a combination of microcosting technique (resource-based accounting method) and hospital list data. Cases were classified as mild, moderate, or severe, and the patients were divided into two groups: the mild group and the moderate-severe group. Classification was determined by the vasoactive inotropic score (VIS), degree of respiratory support, and evidence of organ damage.

Results: The mean age of the cases in the mild group was 6.5±3.7 years, and the mean age of the cases in the moderate-severe group was 9.2±4.3 years. Of 59 patients, 19 (32.2%) were followed up in the pediatric intensive care unit. The median duration of hospitalization in the hospital was 8 (interquartile range: 7-12) days. The total cost of the patients hospitalized with the diagnosis of MIS-C during the study period was 849,242.93$, and the mean cost per patient was 14,393.94±9,631.92$. In the distribution of the total cost of hospitalization according to expenses, the highest rate was pharmacy and blood products (51.99%) and IVIG costs (43.99%). While the mean total cost per person was 13,682.87±8,799.63$ in mild cases, it was 16,433.82±9,440.02$ in moderate-severe cases, and no statistically significant relationship was found between the two groups ($p>0.05$). There was no difference in the mean cost per patient between the cases with and without heart, lung, kidney, or neurologic involvement and advanced respiratory support ($p>0.05$). There was a strong positive correlation between the total costs and age ($r=0.883$, $n=59$, $p<0.0001$), with increased amount of costs with increased age.

Conclusion: In the study, no statistically significant correlation was found between the total cost of per person in the mild group and the moderate-severe group ($p>0.05$). This finding may be due to the wide use of IVIG in MIS-C treatment, in addition to low transfer rates to pediatric intensive care units due to high-flow nasal cannula usage.

Keywords: COVID-19, cost analysis, intravenous immunoglobulin.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in early 2020, caused a health crisis characterized by hyperinflammation symptoms and toxic shock syndrome, such as Kawasaki disease in children, about a year later.[1] The disease called

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multisystem inflammatory syndrome in children (MIS-C) is associated with a poor clinical course with cardiovascular findings, particularly severe circulatory failure requiring intensive care and myocardial involvement and the presence of organ dysfunctions.[2-5] The treatment modalities of MIS-C are mainly based on Kawasaki disease and treatment experience from coronavirus disease 2019 (COVID-19) in adults experiencing cytokine storms. Intravenous immunoglobulin (IVIG) and corticosteroids are used, and advanced treatment protocols, including tumor necrosis factor and interleukin-1 inhibitors and plasmapheresis, are applied in unresponsive cases.[6-13]

The multidisciplinary approach and advanced treatment support required in the management of the disease, which can progress with involvement of many organs, such as the pulmonary, hematological, cardiovascular, renal, and gastrointestinal systems, bring high treatment costs.[14] Due to the technological developments in the field of medicine, the prolongation of people's life spans and the high drug prices, it is important to correctly use economic resources, and limited resources should be exhausted in the most efficient way.[15,16] Demonstration of value has become increasingly important in the current healthcare system.[17] Knowing health cost analyses with cost distributions provides doctors and managers with a systematic and objective perspective in terms of creating alternative healthcare strategies. Hence, this study aimed to evaluate the diagnostic tests and treatments applied in patients with MIS-C and to determine the effect of the disease on health costs.

PATIENTS AND METHODS

This retrospective cohort study was conducted with 59 MIS-C patients (40 males, 19 females; mean age: 7.7±4.2 years; range, 4 months to 16.5 years) at the Health of Sciences Faculty of Medicine Dr. Behçet Uz Children's Hospital between April 1, 2020, and November 1, 2021. The hospital is a referral center for pediatric patients in the Aegean region of Türkiye. The study included all children with MIS-C identified according to the Centers for Disease Control and Prevention guidelines.[18] Patient information was collected using patient files and an electronic record system. Definitive diagnostic criteria are <21 years of age, prolonged fever, elevated inflammatory biomarkers, evidence of clinically severe disease requiring hospitalization, multiple system (>2) organ involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological), evidence of exposure to SARS-CoV-2, and exclusion of other possible diagnoses.[7,18] Exposure to SARS-CoV-2 was assessed in all patients via nasopharyngeal real-time reverse transcription polymerase chain reaction (RT-PCR) analysis or a SARS-CoV-2 antibody test. Exposure to a suspected or confirmed COVID-19 case within four weeks before the onset of clinical manifestations was also recorded.[18] The exclusion of other diagnoses was performed using several microbiological and molecular diagnostic tests, including multiplex polymerase chain reaction tests for common respiratory pathogens, rapid antigen tests for influenza, serological tests for the Epstein–Barr virus, conventional culture tests, including blood culture and throat culture, in addition to peripheral smears and ultrasonography. Sex, age, symptoms at admission, duration of fever, length of hospital stay, intensive care/service follow-up, organ system involvement, examination and laboratory findings, imaging methods, advanced treatment (variables of inotropic drugs, thrombolytic therapy, anticoagulants, antiplatelet agents, biological agent administration, and dialysis-plasmapheresis-transfusion) and respiratory support (>30% oxygen, noninvasive mechanical ventilation, and invasive mechanical ventilation) were investigated. Cases were classified as mild, moderate, or severe, and the patients were divided into two groups: the mild group and the moderate-severe group. Classification was determined by the vasoactive inotropic score (VIS), degree of respiratory support, and evidence of organ damage.[19] Mild cases had no vasoactive requirement, minimal respiratory support, or minimal signs of organ damage. In moderate cases, there was a VIS of ≤10, significant supplemental oxygen requirement, or mild or isolated organ injury. In severe cases, there was moderate or severe organ damage, including a VIS >10, noninvasive or invasive ventilation support, or moderate to severe ventricular dysfunction.[20]

Cost analysis

Demographic and clinical features with hospital costs and length of stay were retrospectively reviewed from the medical files and computerized system of the hospital. Direct medical care costs items were calculated from the hospital perspective using a combination of microcosting technique (resource-based accounting method) and hospital list data. The direct medical costs mainly included charges for inpatient, laboratory, imaging, antimicrobial drugs, consultations, IVIG costs, and transfusion costs. Attributable length of stay for hospital admission was considered as the span of days for the treatment of MIS-C and its complication if happened. The investigators recorded the costs initially in Turkish lira (TL) and converted them to US dollars ($) according to the average TL to US dollars exchange rate between April 1, 2020, and April 1, 2022 (1$=7.7784 TL). During the study, we applied equal discounting of costs and health effects, which was supported by Weinstein and Stason's[21] consistency thesis and the "time neutrality" by Lipscomb et al.[22] The costs were directly obtained from billing the information sent to the social security system.

Statistical analysis

Descriptive analysis of the data was carried out using IBM SPPS version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using Fisher exact and Pearson's chi-square test. The Mann-Whitney U test or the t-test was used to compare numerical variables depending on whether they showed normal distribution. Categorical variables were given as frequencies and percentages, whereas continuous variables were shown as means ± standard deviation. The relationship between total costs (as measured by $) and age (years) was investigated using the Spearman correlation coefficient. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity.

RESULTS

Forty-six (78%) of the patients were previously healthy. Among 59 patients with MIS-C, five (8.5%) had positive RT-PCR results for SARS-CoV-2. The history of contact with a COVID-19 case was detected in 54.2% of MIS-C cases (n=32). Forty-eight (81.4%) patients tested positive for COVID-19 immunoglobulin G, and four (6.8%) patients tested positive for COVID-19 immunoglobulin M (Table 1).

The rate of fever, hypotension, tachycardia, and other symptoms of the patients with MIS-C

The fever was present in all the patients and the median fever duration was 5 (interquartile range [IQR]: 4-7) days. The most common involved organ system was the gastrointestinal system (n=41, 69.5%) and mucocutaneous symptoms (n=37, 62.7%). The symptoms and involved organ systems of the patients are summarized in Table 1. Among the patients, 20.3% (n=12) had hypotension, and 22.1% (n=16) of the patients had tachycardia. The symptoms of the patients were summarized in Table 1. Eight (13.6%) patients had difficulty breathing. Chest radiography showed infiltration/opacity in the lung parenchyma in 15 (25.4%) patients and pleural effusion in seven (11.9%) patients. Cardiovascular system involvement was observed in all patients with pleural effusion on chest X-ray ($p<0.05$). Systolic dysfunction was seen in 11 (18.8%) patients. Coronary artery involvement was seen in two (3.4%) patients. Pericardial effusion was present in three (5.1%) patients. Anemia (30.5%), neutrophilia (40.7%), lymphopenia (61%), and thrombocytopenia (35.6%) were seen in laboratory parameters. There were significant elevations in acute phase values, such as C-reactive protein (96.6%), ferritin (67.8%), fibrinogen (88.1%), and D-dimer (76.3%). Troponin I was elevated in 27.1% of patients. The ratio of positive laboratory findings of the MIS-C patients are reviewed in Table 2.

Thirty-three (55.9%) cases were mild, 26 (44.1%) cases were moderate-severe. There was a statistically significant relationship between the age of the cases and the severity of the disease ($p<0.05$). The mean age of the cases in the mild group was 6.5±3.7 years, and the mean age of the cases in the moderate-severe group was 9.2±4.3 years.

Treatment modalities

The most common treatment was IVIG, which was given to 57 (96.6%) patients in this study.

Table 1. Demographic, clinical, laboratory and treatment characteristics of children with MISC

	n	%	Mean±SD	Median	IQR
Demographic characteristics					
Age (year)			7.7±4.2		
Sex					
Male	40	67.8			
Comorbidity	13	22			
Days in PICU			4.05±1.80		
Death	0	0			
Clinical characteristics					
Fever	59	100			
Days of fever				5	4-7
Respiratory		27.1			
Cough	7	11.9			
Respiratory distress	8	13.6			
Hematological		83.1			
Elevated D-dimer	45	76.3			
Anemia	18	39.5			
Thrombocytopenia	21	35.6			
Lymphopenia	36	61			
Gastrointestinal		69.5			
Vomiting	29	49.2			
Diarrhea	20	33.9			
Abdominal pain	15	25.4			
Skin and mucous membranes		62.7			
Rash	27	45.8			
Edema of the extremities	5	8.5			
Periungual desquamation	6	10.2			
Conjunctival injection	29	49.2			
Neurological disorders		15.3			
Headache	5	8.5			
Neurocognitive disorders	6	10.2			
Other					
Cervical lymphadenopathy	9	15.3			
Renal		35.6			
Acute kidney injury	21	35.6			
Cardiovascular		67.8			
Chest pain	4	6.8			
Shock	20	33.9			
Hypotension	12	20.3			
Tachycardia	16	27.1			
Systolic dysfunction	11	18.8			
Coronary artery dilatation or aneurysm	2	3.4			
Mitral regurgitation	28	47.5			
Aortic regurgitation	5	8.5			
Pericardial effusion	3	5.1			

Table 1. Continued

	n	%	Mean±SD	Median	IQR
SARS-COV-2 labs	59	100			
Positive PCR	5	8.5			
Positive serology					
IgM	4	6.8			
IgG	48	81.4			
Treatment					
Immunoglobulin	57	96.6			
Steroids	26	44.1			
Antiplatelet drugs	35	59.3			
Anticoagulants	33	55.9			
Antivirals	2	3.5			
Vasoactive drugs	16	27.1			
Respiratory support	14	23.7			
Oxygen with mask >30%	4	6.8			
HFNC	6	10.2			
NIMV	4	6.8			
IMV	0	0			
Dialysis (RRT)	1	1.7			
Severity score					
Mild	33	55.9			
Moderate-Severe	26	44.1			

MISC: Multisystem inflammatory syndrome in children; SD: Standard deviation; IQR: Interquartile range; PICU: Pediatric intensive care unit; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; Ig: Immunoglobulin; HFNC: High-flow nasal cannula; NIMV: Noninvasive mechanical ventilation; IMV: Invasive mechanical ventilation; RRT: Renal replacement therapy.

A corticosteroid was added to the treatment of 26 (44.1%) patients. Low molecular weight heparin was administered to 35 (59.3%) patients, and acetylsalicylic acid was given to 33 (55.9%) patients. IVIG + corticosteroid treatment was initiated for 55.6% of patients. Respiratory support was given to 14 (24.7%) patients whose clinical condition deteriorated. Inotropic drugs were administered to 16 (27.1%) of 20 (33.9%) patients who developed shock during the follow-up. Plasmapheresis was performed in one patient.

Of 59 patients, 19 (32.2%) were followed up in the pediatric intensive care unit (PICU), and 40 (67.8%) patients were followed up in the pediatric infectious diseases ward (Table 1). The median duration of hospitalization was 8 (IQR: 7-12) days, and the mean duration of PICU stay of 19 patients was 4.05±1.80 (range, 1 to 7) days.

Table 2. Evaluation of laboratory findings in patients diagnosed with MIS-C (n=59)

Laboratory finding	n	%
Anemia (g/dL)†	18	30.5
Leukocytosis (10^3/uL)†	10	16.9
Lymphopenia (10^3/uL)‡	36	61
Thrombocytopenia (<150 10^3/uL)	21	35.6
Creatine elevation (mg/dL)†	20	33.9
Albumin (<3 g/dL)	7	11.9
C-reactive protein (>0.5 mg/dL)	57	96.6
Ferritin (>200 µg/L)	40	67.8
Troponin (>0.06 ng/mL)	16	27.1
Fibrinogen (>400 mg/dL)	52	88.1
D-dimer (>500 ng/mL)	45	76.3

MIS-C: Multisystem inflammatory syndrome in children; † Values higher than the age-appropriate level range were accepted. ‡ Values below 3000 µL for those <1 year and 1000 µL for those >1 year were accepted.

Table 3. Distribution of cost by expenses

Variables	Total cost ($)	Cost per patient ($)
		Mean±SD
Total cost	849,242.93	14,393.94±9,631.92
IVIG cost	362,028.74	6,136.07±511.39
Other pharmacy and blood products	431,725.89	7,703.09±657.88
Inpatient floor costs	276,481.91	602.48±82.87
Medical consumable costs	9,048.68	19.71±3.13

IVIG: Intravenous immunoglobulin; SD: Standard deviation.

Cost analysis

The total cost of the patients hospitalized with the diagnosis of MIS-C during the study period was 849,242.93$, and the mean cost per patient was 14,393.94±9,631.92$. The total cost was analyzed under four headings: IVIG, other pharmacy and blood products, inpatient floor cost (including laboratory, consultation, and radiological examinations), and medical consumables cost (Table 3). In the distribution of the total cost of hospitalization according to expenses, the highest rate was pharmacy and blood products (51.99%) and IVIG costs (43.99%; Table 3).

In the relationship between the clinical level and the total follow up cost, the mean total cost per person was 13,682.87±8,799.63$ in mild cases, while it was 16,433.82±9,440.02$ in moderate-severe cases, and no statistically significant relationship was found ($p>0.05$, Table 4). There was no difference in the mean cost per patient between patients with and without heart, lung, kidney, or neurologic involvement and advanced respiratory support ($p>0.05$, Table 4).

There was a strong positive correlation between the two variables ($r=0.883$, $n=59$, $p<0.0001$), with the amount of costs increased with age.

Table 4. Evaluation of the relationship between disease severity and organ system involvement with the total cost per person

		Total cost ($)		
Variables*	n	Mean±SD	t	*p*
Disease severity			-1.155	0.253
Mild	33	13,682.87±8,799.63		
Moderate-severe	26	16,422.06±9,440.02		
Cardiovascular system involvement			-1.573	0.121
Yes	40	16,164.93±9,253.75		
No	19	12,221.95±8,419.10		
Respiratory system involvement			0.044	0.965
Yes	16	14,809.48±8,330.06		
No	43	14,927.04±9,480.26		
Renal system involvement			-0.719	0.478
Yes	21	16,180.95±11,380.82		
No	38	14,184.58±7,660.72		
Neurological system involvement			-1.802	0.077
Yes	7	20,612.05±8,351.03		
No	52	14,125.57±9,007.36		

* Independent samples t-test.

DISCUSSION

In this study, we shared our experience with MIS-C and analyze the effect of the intensive treatment process on the health cost.

The total cost of followed 59 MIS-C patients within one year was 849,242.93$. In the study, no statistically significant correlation was found between the total cost of per person follow-up in the mild group and the moderate-severe group ($p>0.05$, Table 4). We think this finding is due to the IVIG treatment, which was given nearly to all patients and consisted of the most important item in the breakdown analysis of costs. In addition, in our institution, IVIG was the standard treatment modality in the mild, moderate, and severe cases of MIS-C, which is very expensive and occasionally inaccessible in our country.

It was observed that organ system involvement did not create a statistically significant difference on total cost ($p>0.05$, Table 4). The mean cost of the cases with cardiovascular and neurological system involvement were similar to cases without the involvement of these systems, although this difference was not statistically significant. In contrast with our findings, a comprehensive study of 4107 MIS-C patients reported that the cost nearly tripled as the number of affected organ systems increased.[23] We think that it would be valuable to ensure homogeneity between groups by increasing the number of samples in ongoing studies to further support the results related to neurological system involvement. It was determined that receiving respiratory support did not have a statistically significant additive effect on the total cost of the cases. On the other hand, a significant portion of our patients receiving respiratory support used oxygen support with a high-flow nasal cannula, preventing some of the patients from transferring to the PICU, which also decrease the healthcare costs. A previous study from our center reported that 25.9% of the patients with MIS-C were followed up in the PICU, which was lower compared to previous studies.[24-28] We believe that using a high-flow nasal cannula and the lower admission rate to the PICU were factors decreasing the costs.

IVIG treatment, reported as the first-line therapy for all clinical severity levels of the disease,[29] was applied to 96.6% of our patients. In the literature, the use of IVIG treatment varies between 71 and 100%.[5,11,24,30-33] This may be related to the relatively high use of biological agents and steroids.[5,34,35] In addition, with early IVIG replacement applied to patients in our center, a rapid improvement in the clinic and fewer disease-related complications were noticed; consequently, an approach aimed primarily at the use of IVIG was adopted. Cardiovascular system complications and intensive care hospitalization rates are lower in our center compared to other studies, and our mortality rate of 0% also supports this. IVIG replacement applied alone has left its place to IVIG + steroid combined treatment over time. Belhadjer et al.[12] emphasized that cardiovascular recovery develops faster with combined therapy. Similarly, in a retrospective study, it was reported that more positive results were obtained with combined treatment.[36] In our study, 44.1% of the patients received combined treatment. Hypotension, systolic dysfunction, thrombocytopenia, lymphopenia, and need for intensive care were found to be significantly higher in these patients. Furthermore, there was no significant relationship between tachycardia and the clinical level of the cases ($p>0.05$) and the use of combined treatment ($p>0.05$). Devrim et al.[37] also reported the existence of a significant relationship between the use of combined therapy and existing variables ($p=0.014$). We believe that the lack of a relationship between the clinical level and the use of combined therapy is related to the inhomogeneity of the medium-severe group. In another study, steroid treatment was started in 42% of severe cases and 45% of mild cases, and there was no significant relationship between the clinical level of the patients and the use of steroid therapy.[5] Our findings are important in terms of showing that IVIG + steroid treatment is given with appropriate indications in our center and that the cases given this treatment have clinical severity enough to be candidates for intensive care. Although the exact criteria for the use of IVIG+steroid therapy has not been determined, it is also supported by the literature that this treatment should be started in patients with decreased ejection fraction and presence of hypotension and respiratory failure, which are included in the definition of moderate and severe MIS-C.[38]

The median hospital follow-up of our patients was 8 (IQR: 7-12) days, and a statistically significant correlation was found between the severity of the disease and the total hospital follow-up time ($p<0.01$). Similar hospitalization rates are reported in the literature[37,39,40] Forty (67.8%) of the patients were followed in the ward, and 19 (32.2%) were followed in the intensive care unit, and the mean intensive care follow-up of the patients was 4.05±1.80 (range, 1 to 7) days. Although the follow-up times of patients in the intensive care unit are similar in the literature,[32,37,41] there are studies reporting higher rates of intensive care follow up in international data.[28,35] In a systemic review by Kaushik et al.,[35] 68% of the patients needed intensive care, and the median follow-up time was 5 (IQR: 4-8) days. We believe that the data differences between the countries on this subject are related to the lack of a universal algorithm for admission to the intensive care unit, the differences between the organization of hospitals, and the capacities of the intensive care unit. Despite this difference in the hospitalization rates of the patients, the fact that the follow-up periods are similar supports this. Mortality rates varying between 0.8 and 2.0% have been reported in the literature.[3,5,24,32-34,42] In our study, the mortality rate was 0%.[30,43,44]

This study has several limitations due to the retrospective collection of data. Additionally, our sample size is small to generalize our findings; however, given the limited number of studies focusing on MIS-C, our study provides additional useful data to assist clinicians in the early identification of patients who need further investigation and treatment.

In conclusion, this is the first study to perform the cost analysis of MIS-C in the literature and reveal that MIS-C requires costly treatment strategies due to severe myocardial dysfunction and multiorgan failure. We believe that knowing the cost of follow-up and the associated findings in this disease, which covers an important area in health economics, will guide the definition of the economic burden in the healthcare system.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Dr. Behçet Uz Pediatric Diseases and Surgery Hospital Clinical Research Ethics Committee (date: 08.10.2020, no: 2020/14-06). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8. doi: 10.1016/S0140-6736(20)31094-1.
2. Feng Z, Bao Y, Yang Y, Zheng Y, Shen K. Severe acute respiratory syndrome coronavirus 2-induced multisystem inflammatory syndrome in children. Pediatr Investig 2020;4:257-62. doi: 10.1002/ped4.12225.
3. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol 2021;56:837-48. doi: 10.1002/ppul.25245.
4. Williams V, Dash N, Suthar R, Mohandoss V, Jaiswal N, Kavitha TK, et al. Clinicolaboratory profile, treatment, intensive care needs, and outcome of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2: A systematic review and meta-analysis. J Pediatr Intensive Care 2020;11:1-12. doi: 10.1055/s-0040-1719173.
5. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: A systematic review. Eur J Pediatr 2021;180:2019-34. doi: 10.1007/s00431-021-03993-5.
6. World Health Organization Scientif Brief: Multisystem inflammatory syndrome in children and adolescents with COVID-19. Available at: World Health Organization Scientif Brief: Multisystem inflammatory syndrome in children and adolescents with COVID-19. [Inter-net]. 2020 May [Cited 2022 Jan]. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

7. Acevedo L, Piñeres-Olave BE, Niño-Serna LF, Vega LM, Gomez IJA, Chacón S, et al. Mortality and clinical characteristics of multisystem inflammatory syndrome in children (MIS-C) associated with covid-19 in critically ill patients: An observational multicenter study (MISCO study). BMC Pediatr 2021;21:516. doi: 10.1186/s12887-021-02974-9.
8. Ouldali N, Pouletty M, Mariani P, Beyler C, Blachier A, Bonacorsi S, et al. Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: A time-series analysis. Lancet Child Adolesc Health 2020;4:662-8. doi: 10.1016/S2352-4642(20)30175-9.
9. Kam KQ, Ong JSM, Lee JH. Kawasaki disease in the COVID-19 era: A distinct clinical phenotype? Lancet Child Adolesc Health 2020;4:642-3. doi: 10.1016/S2352-4642(20)30207-8.
10. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: Prospective multicentre observational cohort study. BMJ 2020;370:m3249. doi: 10.1136/bmj.m3249.
11. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259-69. doi: 10.1001/jama.2020.10369.
12. 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;142:429-36. doi: 10.1161/CIRCULATIONAHA.120.048360.
13. Belot A, Antona D, Renolleau S, Javouhey E, Hentgen V, Angoulvant F, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. Euro Surveill 2020;25:2001010. doi: 10.2807/1560-7917.ES.2020.25.22.2001010.
14. Parums DV. Editorial: Long COVID, or post-COVID syndrome, and the global impact on health care. Med Sci Monit 2021;27:e933446. doi: 10.12659/MSM.933446.
15. Tıraş HH. Sağlık ekonomisi: Teorik bir inceleme. KSÜ Tıp Dergisi 2013;3:125-52.
16. Arslan E, Önder NT, Kayalı S, Keskin Z, Yiğit Ö. Kamu hastanelerinde branş bazında hasta başı maliyet analizi (İstanbul Eğitim ve Araştırma Hastanesi örneği). Sağlık Akademisyenleri Dergisi 2015;2:40-52.
17. Roudsari B, McWilliams J, Bresnahan B, Padia SA. Introduction to cost analysis in IR: Challenges and opportunities. J Vasc Interv Radiol 2016;27:539-45. e1. doi: 10.1016/j.jvir.2015.12.754.
18. CDC. Health Alert Network (HAN): Multisystem Infammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. [Accessed: May 20, 2021].
19. McIntosh AM, Tong S, Deakyne SJ, Davidson JA, Scott HF. Validation of the vasoactive-inotropic score in pediatric sepsis. Pediatr Crit Care Med 2017;18:750-7. doi: 10.1097/PCC.0000000000001191.
20. Jonat B, Gorelik M, Boneparth A, Geneslaw AS, Zachariah P, Shah A, et al. Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 in a children's hospital in New York city: Patient characteristics and an institutional protocol for evaluation, management, and follow-up. Pediatr Crit Care Med 2021;22:e178-91. doi: 10.1097/PCC.0000000000002598.
21. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977;296:716-21. doi: 10.1056/NEJM197703312961304.
22. Lipscomb J, Torrance G, Weinstein M. Time preference. In Gold M, Siegel J, Russel LB, Weinstein MC (eds). Cost-effectiveness in health and medicine. Oxford University Press. 1996.
23. Encinosa W, Moon K, Figueroa J, Elias Y. Complications, adverse drug events, high costs, and disparities in multisystem inflammatory syndrome in children vs COVID-19. JAMA Netw Open 2023;6:e2244975. doi: 10.1001/jamanetworkopen.2022.44975.
24. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074-80. doi: 10.15585/mmwr.mm6932e2.
25. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 2021;325:1074-87. doi: 10.1001/jama.2021.2091.
26. Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): Report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. Int J Infect Dis 2020;100:75-81. doi: 10.1016/j.ijid.2020.08.062.
27. Venkataraman A, Kumar NP, Hanna LE, Putlibai S, Karthick M, Rajamanikam A, et al. Plasma biomarker profiling of PIMS-TS, COVID-19 and SARS-CoV2 seropositive children - a cross-sectional observational study from southern India. EBioMedicine 2021;66:103317. doi: 10.1016/j.ebiom.2021.103317.
28. Sood M, Sharma S, Sood I, Sharma K, Kaushik A. Emerging evidence on multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection: A systematic review with meta-analysis. SN Compr Clin Med 2021;3:38-47. doi: 10.1007/s42399-020-00690-6.

29. Haslak F, Gunalp A, Kasapcopur O. A cursed goodbye kiss from severe acute respiratory syndrome-coronavirus-2 to its pediatric hosts: Multisystem inflammatory syndrome in children. Curr Opin Rheumatol 2023;35:6-16. doi: 10.1097/BOR.0000000000000910.
30. Ozsurekci Y, Gürlevik S, Kesici S, Akca UK, Oygar PD, Aykac K, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic in Turkey: First report from the Eastern Mediterranean. Clin Rheumatol 2021;40:3227-37. doi: 10.1007/s10067-021-05631-9.
31. 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;143:21-32. doi: 10.1161/CIRCULATIONAHA.120.050065.
32. Yilmaz Ciftdogan D, Ekemen Keles Y, Cetin BS, Dalgic Karabulut N, Emiroglu M, Bagci Z, et al. COVID-19 associated multisystemic inflammatory syndrome in 614 children with and without overlap with Kawasaki disease-Turk MIS-C study group. Eur J Pediatr 2022;181:2031-43. doi: 10.1007/s00431-022-04390-2.
33. Miller AD, Zambrano LD, Yousaf AR, Abrams JY, Meng L, Wu MJ, et al. Multisystem inflammatory syndrome in children-United States, February 2020-July 2021. Clin Infect Dis 2022;75:e1165-75. doi: 10.1093/cid/ciab1007.
34. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev 2021;38:51-7. doi: 10.1016/j.prrv.2020.08.001.
35. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A Systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J 2020;39:e340-6. doi: 10.1097/INF.0000000000002888.
36. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA 2021;325:855-64. doi: 10.1001/jama.2021.0694.
37. Devrim İ, Böncüoğlu E, Kıymet E, Şahinkaya Ş, Çelebi MY, Cem E, et al. A retrospective comparative analysis of factors affecting the decision and outcome of initial intravenous immunoglobulin alone or intravenous immunoglobulin plus methylprednisolone use in children with the multisystem inflammatory syndrome. Pediatr Rheumatol Online J 2022;20:69. doi: 10.1186/s12969-022-00726-2.
38. Mahmoud S, Fouda EM, Kotby A, Ibrahim HM, Gamal M, El Gendy YG, et al. The "Golden hours" algorithm for the management of the multisystem inflammatory syndrome in children (MIS-C). Glob Pediatr Health 2021;8:2333794X21990339. doi: 10.1177/2333794X21990339.
39. 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. doi: 10.1016/j.eclinm.2020.100527.
40. Alkan G, Sert A, Oz SKT, Emiroglu M, Yılmaz R. Clinical features and outcome of MIS-C patients: An experience from Central Anatolia. Clin Rheumatol 2021;40:4179-89. doi: 10.1007/s10067-021-05754-z.
41. Kıymet E, Böncüoğlu E, Şahinkaya Ş, Cem E, Çelebi MY, Düzgöl M, et al. A comparative study of children with MIS-C between admitted to the pediatric intensive care unit and pediatric ward: A one-year retrospective study. J Trop Pediatr 2021;67:fmab104. doi: 10.1093/tropej/fmab104.
42. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York state. N Engl J Med 2020;383:347-58. doi: 10.1056/NEJMoa2021756.
43. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr 2020;224:141-5. doi: 10.1016/j.jpeds.2020.06.044.
44. García-Salido A, de Carlos Vicente JC, Belda Hofheinz S, Balcells Ramírez J, Slöcker Barrio M, Leóz Gordillo I, et al. Severe manifestations of SARS-CoV-2 in children and adolescents: From COVID-19 pneumonia to multisystem inflammatory syndrome: A multicentre study in pediatric intensive care units in Spain. Crit Care 2020;24:666. doi: 10.1186/s13054-020-03332-4.