flora

RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2022;27(1):158-176 • doi: 10.5578/flora.20229912

Assessment of Features of MIS-C and Non-MIS-C Patients: Meta-Analysis

MIS-C ve MIS-C Olmayan Hastaların Özelliklerinin Değerlendirilmesi: Meta-Analiz

Caner BAYSAN[1](İD), Meltem ÇÖL[1](İD), Saliha AYDIN[1](İD), Sibel GÜRBÜZ[1](İD), Caner ÖZDEMİR[1](İD), Türker BEKAR[1](İD), Erkan BÜYÜKDEMİRCİ[2](İD)

[1] Department of Public Health, Ankara University Faculty of Medicine, Ankara, Turkey
[2] Public Health Services, Ankara Provincial Health Directorate, Ankara, Turkey

Cite this article as: *Baysan C, Çöl M, Aydın S, Gürbüz S, Özdemir C, Bekar T, et al. Assessment of features of MIS-C and non-MIS-C patients: meta-analysis. FLORA 2022;27(1):158-76.*

ABSTRACT

Introduction: *Pediatric COVID-19 cases are typically known to be mildly symptomatic and show a good prognosis. However, more severe condition termed Multisystem inflammatory syndrome (MIS-C) is encountered in children. This research aimed to evaluate the differences between MIS-C and non-MIS-C (children who were infected with SARS-CoV-2 but did not develop MIS-C) patients according to demographics, comorbidities, and symptoms conditions, as well as clinical, laboratory, radiological findings, treatment, and prognosis.*

Materials and Methods: *This systematic review and meta-analysis were performed in accordance with PRISMA guidelines using electronic databases of PubMed, Scopus, Science-Direct, and LitCovid including articles on observational studies comparing the MIS-C and non-MIS-C cases published between 01 January 2020-15 January 2021.*

Results: *Seventeen articles meeting the criteria were included. No difference was found in terms of gender and age from the demographic characteristics of the MIS-C and non-MIS-C groups. Black race and clinical findings such as fever, rash, fatigue, loss of appetite, vomiting and diarrhea, and laboratory findings CRP and ferritin were found to be higher in the MISC group compared to the nonMISC group ($p<0.05$). Cardiac complications, use of some medical treatments (steroids, IVIG, inotropic therapy), and need for intensive care were also higher ($p< 0.05$). Conversely, the presence of comorbidity, presence of rhinorrhea, hemoglobin, lymphocyte, and platelet values were higher in the non-MIS-C group ($p< 0.05$).*

Conclusion: *Evaluation of MIS-C and non-MIS-C patients for various characteristics revealed differences that will guide the diagnosis of and approach to MIS-C cases.*

Key Words: *Pediatric COVID-19; Mis-c; Meta-analysis; Demographic features; Inflammatory markers*

Received/Geliş Tarihi: 14/10/2021 - Accepted/Kabul Ediliş Tarihi: 26/11/2021

Available Online Date: 24.03.2022

ÖZ

MIS-C ve MIS-C Olmayan Hastaların Özelliklerinin Değerlendirilmesi: Meta-Analiz

Caner BAYSAN[1], Meltem ÇÖL[1], Saliha AYDIN[1], Sibel GÜRBÜZ[1], Caner ÖZDEMİR[1], Türker BEKAR[1], Erkan BÜYÜKDEMİRCİ[2]

[1] Ankara Üniversitesi Tıp Fakültesi, Halk Sağlığı Anabilim Dalı, Ankara, Türkiye
[2] Ankara İl Sağlık Müdürlüğü, Halk Sağlığı Hizmetleri, Ankara, Türkiye

Giriş: *Pediatrik COVID-19 vakalarının tipik olarak hafif semptomatik olduğu ve iyi bir prognoz gösterdiği bilinmektedir. Ancak çocuklarda multisistem inflamatuvar sendrom (MIS-C) olarak adlandırılan daha şiddetli bir durumla karşılaşılmaktadır. Bu araştırma, MIS-C ve MIS-C olmayan (SARS-CoV-2 ile enfekte olan ancak MIS-C gelişmeyen çocuklar) hastaların demografik, komorbidite ve semptom özellikleri yanı sıra klinik, laboratuvar, radyolojik bulgular, tedavi ve prognoz farklılıklarının değerlendirilmesini amaçlamaktadır.*

Materyal ve Metod: *Bu sistematik derleme ve meta-analiz, Ocak 2020-15 Ocak 2021 arasında PubMed, Scopus, Science-Direct ve LitCovid elektronik veritabanlarındaki MIS-C ve MIS-C olmayan hastaları karşılaştıran gözlemsel çalışmalara ilişkin makaleler kullanılarak PRISMA rehberine göre yapılmıştır*

Bulgular: *Kriterleri karşılayan 17 makale dahil edildi. MIS-C ve non-MIS-C gruplarının demografik özelliklerinden cinsiyet ve yaş bakımından fark saptanmamış olup, MIS-C grubunda siyah ırk olma olasılığı ve klinik bulgulardan ateş, döküntü, yorgunluk, iştah kaybı, kusma ve ishal, laboratuar bulgulardan CRP ve ferritin non-MIS-C grubuna göre daha yüksek bulunmuştur (p< 0,05). MIS-C grubunda kardiyak komplikasyonlar, bazı medikal tedavilerin kullanımı (steroid, IVIG, inotropik tedavi) ve yoğun bakım ihtiyacı daha yüksek bulunmuştur (p< 0,05). Buna karşılık, MIS-C olmayan grupta komorbidite varlığı, rinore varlığı daha fazla, hemoglobin, lenfosit ve trombosit değerleri daha yüksekti (p< 0,05).*

Sonuç: *MIS-C ve MIS-C olmayan hastaların çeşitli özellikler açısından değerlendirilmesi, MIS-C vakalarının teşhisine ve yaklaşıma yön verecek farklılıkları ortaya çıkarmıştır.*

Anahtar Kelimeler: *Pediatrik COVID-19; Mis-c; Meta-analiz; Demografik özellikler; İnflamatuar belirteçler*

INTRODUCTION

Pediatric COVID-19 cases generally have a mild course and show good prognosis and prevalence varies by country. The World Health Organization (WHO) states that approximately 8.5% of reported cases are children. The American Academy of Pediatrics has reported that 13.4% of COVID-19 cases, 1.3-3.1% of hospitalized patients, and 0.0-0.19% of deaths were children in the United States[1,2].

Initially, COVID-19 reports have shown that most children had mild or asymptomatic disease[3]. However, children and adolescent groups with a multisystem inflammatory condition requiring admission to intensive care units with some features similar to Kawasaki disease and toxic shock syndrome have been reported later[4,5]. This clinical condition has been termed COVID-19 related to multisystem inflammatory syndrome in children (MIS-C). WHO, Centers for Disease Control and Prevention (CDC) and the Royal College of Pediatrics and Child Health (RCPCH) have created diagnostic criteria for MIS-C[6-8]. These criteria include persistent fever, rash, multisystem organ involvement, inflammatory laboratory findings, positive test results or suspected contact for SARS-CoV-2 are prominent. The present findings support that MIS-C emerges two to four weeks after SARS-CoV-2 infection. Although the etiopathogenesis is yet to be discovered, virus-induced post-infective immune dysregulation is thought to play an important role[9,10].

Distinguishing MIS-C cases from COVID-19 cases will aid in the decrease of disease-related morbidity and mortality, and research on this subject is restricted.

Thus, in this meta-analysis, it is expected to uncover differences in terms of symptoms, clinical, laboratory, and radiographic findings, treatment, and prognosis between MIS-C and non-MIS-C patients in addition to demographic characteristics and the presence of comorbidity.

MATERIALS and METHODS

This systematic review and meta-analysis were performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline.

Search Strategy

A systematic review of literature using PubMed, Scopus, Science-Direct and Litcovid electronic databases was conducted. For screening, the keywords "COVID-19" or "severe acute respiratory syndrome coronavirus 2" or "SARS-CoV-2" or "2019-nCoV" and "multisystem inflammatory syndrome in children" or "pediatric multisystem inflammatory syndrome" or "Kawasaki-like disease" or "MIS-C" were used as text terms.

Two review authors reviewed the titles and abstracts of the studies found in the above sources, excluding duplicates. If the screening process from titles and abstracts alone failed, full texts were obtained. The studies to be included in the meta-analysis were determined following a reevaluation of the conflicts with another researcher.

Inclusion and Exclusion Criteria

Observational analytical (case-control, cohort, cross-sectional) studies in children comparing the cases of MIS-C and non-MIS-C (children who were infected with SARS-CoV-2 but did not develop MIS-C) published between January 01, 2020 and January 15, 2021, written in English and whose full text can be accessed were included in the study. Systematic or narrative reviews, meta-analysis, guideline, opinion letters, editor letters, case reports, case series, experimental studies, studies on adult patients, and studies without MIS-C comparison were excluded.

Data Extraction

For each eligible study, three pairs of reviewers, independently, abstracted the following information on study characteristics (year of publication, country, medical center); population characteristics (sample size, context in which the study was conducted and other population characteristics). Demographic, clinical and radiological characteristics, laboratory findings, treatment and prognosis differences of MIS-C and non-MIS-C cases were examined. In the selected studies, MIS-C criterion was generally defined as WHO, CDC and RCPCH criteria. Non-MIS-C patients are primarily symptomatic moderate-to-severe cases who have been admitted to the hospital. While the non-MIS-C group was divided into mild and severe in 3 studies, it was stated as respiratory and non-respiratory in one study (Table 1)[11-14]. For categorical variables, group data other than MIS-C were combined. Studies with multi-group comparison in the evaluation of continuous variables were not included in the analysis. In studies involving children and adults, only data belonging to children were analyzed. In the studies conducted in the same health center at overlapping times, the research containing more data for each variable was analyzed[11,12,15-17]. For laboratory findings, different units used for D-dimer and CRP have been converted into a common unit. For continuous variables, the values given as median, minimum, maximum and interquartile range were converted to mean and standard deviation[18,19].

Quality Assessment

Quality assessment of the included research studies was completed by three researchers using the Newcastle-Ottawa Scale (NOS) in accordance with the type of research[20].

Data Analysis

The analyzes were carried out using the "Meta" package of 3.6.1 version of the R software program[21]. The meta-analysis findings were shown with forest plot graphics. For continuous outcome data, means and standard deviations were used to calculate a mean difference (MD). For dichotomous outcomes, the odds ratio (OR) was calculated. The Egger test was used to evaluate publication bias[22]. The heterogeneity of the selected studies was evaluated with the I^2 test. Fixed effect model was used for the analysis of the data with 0% heterogeneity, and the random effect model was used for the evaluation of the data with >0%. Statistical significance level was accepted as <0.05.

RESULTS

As a result of the research strategy, 1531 articles were identified (PubMed= 324, Litcovid= 639, Scopus= 223 and Science Direct= 345).

Table 1. Characteristics of the included studies

Author, Year	Journal	Study region	Determined age range	Participants, no*. (MIS-C-non-MIS-C)	Non-MIS-C group features	Quality assessment score
Diorio et al. 2020[11]	Blood Advances	USA/ Philadelphia	5-17***	18-32**	Minimal (n= 21)/ Severe (n= 11) COVID-19	7
Anderson et al. 2020[12]	Journal of the Pediatric Infectious Diseases Society	USA/ Philadelphia	3.5y-17y***	10-19**	Minimal (n= 10)/ Severe (n= 9) COVID-19	7
Del Borrello et al. 2020[13]	Journal of Thrombosis and Haemostasis	Italy/Turin	0-21	6-30**	Mild (14)/ Moderate(10)/ Severe (6) COVID-19	8
Fernandes et al. 2021[14]	The Journal of Pediatrics	USA/New York, New Jersey and Connecticut	≤22	69-212**	Respiratuar (n= 143)/Other (n= 69)	8
Vella et al. 2021[15]	Science Immunology	USA/ Philadelphia	≤18	14-16	Those who applied to the hospital with positive PCR test	7
Rostad et al. 2021[16]	Pediatric Radiology	USA/Atlanta	0-18	11-16	Symptomatic PCR test positive COVID-19	8
Rostad et al. 2020[17]	Pediatrics	USA/Atlanta	0-21	10-10	Symptomatic PCR test positive COVID-19	8
Antúnez-Montes et al. 2020[23]	The Pediatric Infectious Disease Journal	Mexico, Colombia, Peru, Costa Rica and Brazil	≤18	95-314	Those who applied to the hospital with positive PCR test	8
Freeman et al. 2020[24]	medRxiv	USA/ Pennsylvania	<21 for MIS-C <22 for COVID-19	3-19	COVID-19 patients hospitalized	9
Pereira et al. 2020[25]	Clinics	Brazil/São Paulo	<18	6-60	Symptomatic PCR test positive COVID-19	9
Swann et al. 2020[26]	BMJ	UK/England, Wales and Scotland	<19	52-404	Symptomatic PCR test positive COVID-19	8
García-Salido et al. 2020[27]	Critical Care	Spain	<18	45-29	COVID-19 patients followed in the ICU	8
Prata-Barbosa et al. 2020[28]	Jornal de Pediatria	Brazil	1m-19y***	10-69	COVID-19 patients followed in the ICU	9
Weisberg et al. 2021[29]	Nature Immunology	USA/New York	3y-18y***	16-31	Symptomatic PCR test positive COVID-19	7

Table 1. Characteristics of the included studies (continue)

Author, Year	Journal	Study region	Determined age range	Participants, no*. (MIS-C-non-MIS-C)	Non-MIS-C group features	Quality assessment score
Yonker et al. 2020[30]	The Journal of Pediatrics	USA/ Massachusetts	≤22	18-49	Symptomatic PCR test positive COVID-19	7
Consiglio et al. 2020[31]	Cell	Italy/Rome, Sweden/ Stockholm	0-19 for MIS-C	13-41	Symptomatic PCR test positive COVID-19	8
Lee et al. 2020[32]	JAMA Network Open	USA/New York	<21 for MIS-C, <20 for COVID-19	223-717	Active Surveillance data	8

* The number of people included in the analyzes varies according to the variable examined.
** Non-MIS-C group was obtained from the collection of two or more subgroups.
*** There was no age range determined as the criterion of inclusion in the study. The age range of the participants are shown.

Five hundred and seventy-five records that were not duplicated and/or full text articles were issued. Nine hundred and fifty-six full text articles were evaluated for eligibility, 17 articles met the inclusion and exclusion criteria and were included in the meta-analysis. The PRISMA flowchart is shown in Figure 1. Various basic features of the included studies are shown in Table 1.

The meta-analysis results of the selected studies with MIS-C and non-MIS-C groups are given under the titles demographic features, presence of comorbidity, symptoms, laboratory and radiological findings, treatment and outcome.

Demographic Features and Comorbidity

When evaluated in terms of average age, mean age of MIS-C patients was 0.2 years (95% CI= 2.58-2.99) higher. (p= 0.886, I^2=88.0%). When the studies were evaluated in terms of sex distribution; there was no difference between the two groups (Figure 2).

When studies with comparisons of black and white race were analyzed, MIS-C patients were more likely to be black (OR= 1.84, 95% CI= 1.17-2.90, I^2= 11.4%). In terms of ethnicity, it was determined that MIS-C patients were 50% less likely to be Hispanic than non-MIS-C group patients (OR=0.50, 95% CI= 0.31-0.80), p< 0.001, I^2= 0%).

Any pre-existing or concomitant disease, such as respiratory, cardiac, neurological, or immunosuppressed state, is considered a comorbidity. The probability of comorbidity was found to be lower in MIS-C patients (OR= 0.39, 95% CI= 0.27-0.58, p< 0.001, I^2=0%) (Figure 3).

Considering the studies evaluating asthma and obesity for MIS-C patients and non-MIS-C patients, there is no difference between the presence of asthma and presence of obesity. Body mass index (BMI) mean difference of MIS-C patients was 1.86 kg/m2 higher (95% Cl=-11.61-15.34) than non-MIS-C patients, but there was no statistically significant difference (p= 0.787, I^2= 92.1%).

Symptoms

Symptoms such as fever (OR= 7.17, 95% CI= 2.16-23.83), rash (OR= 9.25, 95% CI= 5.09-16.83), vomiting (OR= 8.00, 95% CI= 4.70-13.64), diarrhea (OR= 7.71, 95% CI= 4.14-14.39), gastrointestinal (GIS) symptoms (OR= 2.66, 95% CI= 1.22-5.75), refusal to eat (OR= 4.07, 95% CI= 2.55-6.49), fatigue (OR= 3.02, 95% CI= 1.86-4.90) was detected to be higher in MIS-C patients than non-MIS-C patients (Figures 4,5).

Rhinorrhea is less common in patients with MIS-C than in the other group (OR= 0.17, 95% CI= 0.07-0.42, p< 0.001, I^2= 0%). There was no difference between the two groups in terms of the presence of myalgia in current studies with high heterogeneity (OR= 2.53, 95% CI= 0.20-31.61, p= 0.472, I^2= 86.3%).

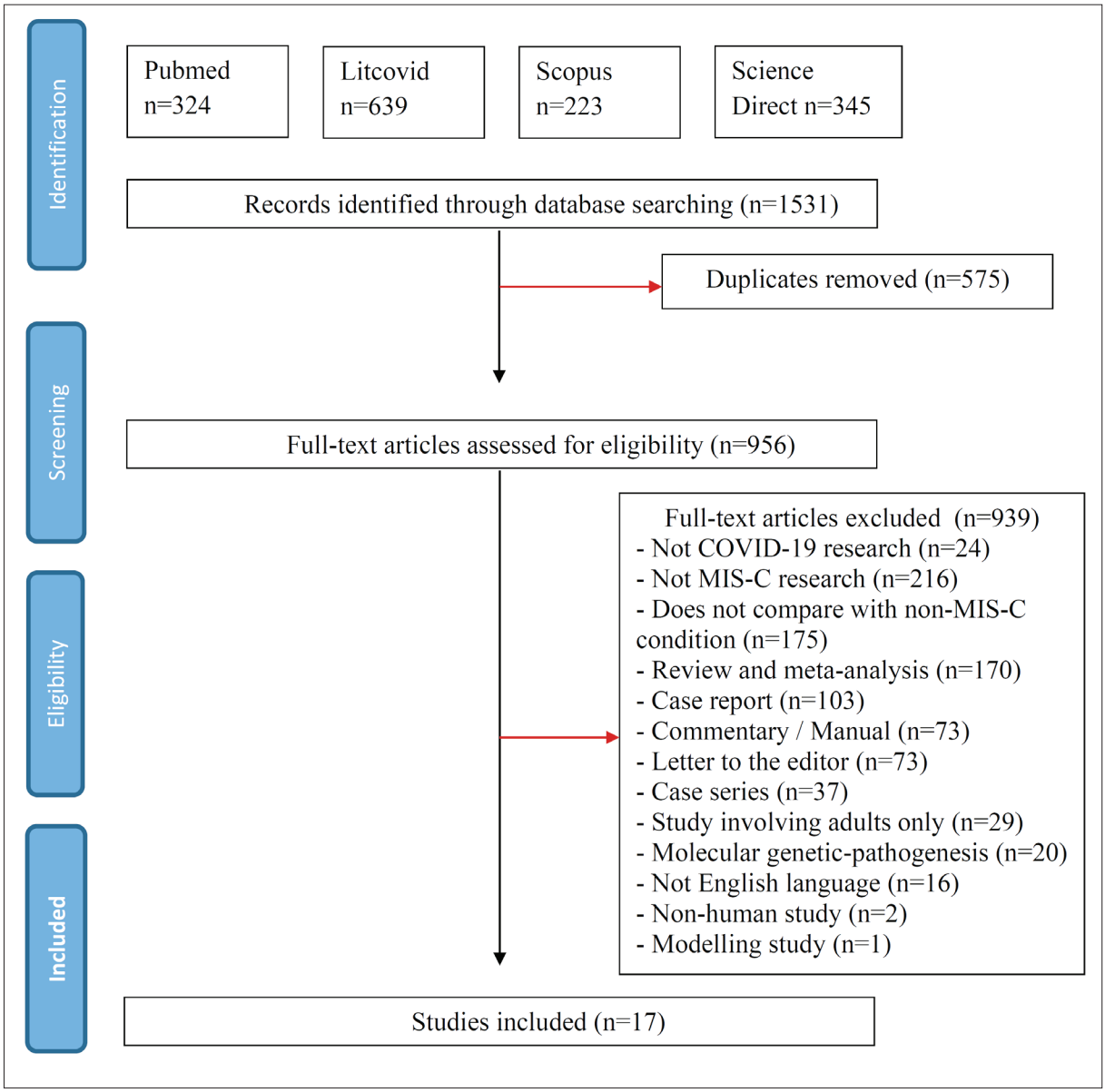

Figure 1. PRISMA flowchart.

There was no statistically significant difference between the groups in terms of dyspnea, cough, headache, and seizure symptoms. Heterogeneity in each of the available studies is above 60% (Table 2).

Laboratory Findings

Mean hemoglobin (Hb) value of MIS-C patients was found to be statistically significantly 0.75 mg/dL lower than the non-MIS-C group (95% CI= -1.48;-0.02, p= 0.045, I^2= 0%). Mean white blood cell (WBC) value of MIS-C patients was 792.7 count/per microliter was higher than the non-MIS-C group yet not statistically significant (p= 0.681, I^2= 70.1%, 95% CI= -2990.58;4575.96). Lymphocyte and platelet values of MIS-C patients, when compared to the non-MIS-C group, was found to be statistically lower (MD= -1242.10 lymphocytes/mcL, 95% CI= -1868.03;-616.17, I^2= 66.0% and MD= 90.90x10^3 platelet/mcL, 95% CI= -127.87x10^3;-53.93x10^3, I^2= 19.4% respectively) (Figure 6). When inflammatory marker

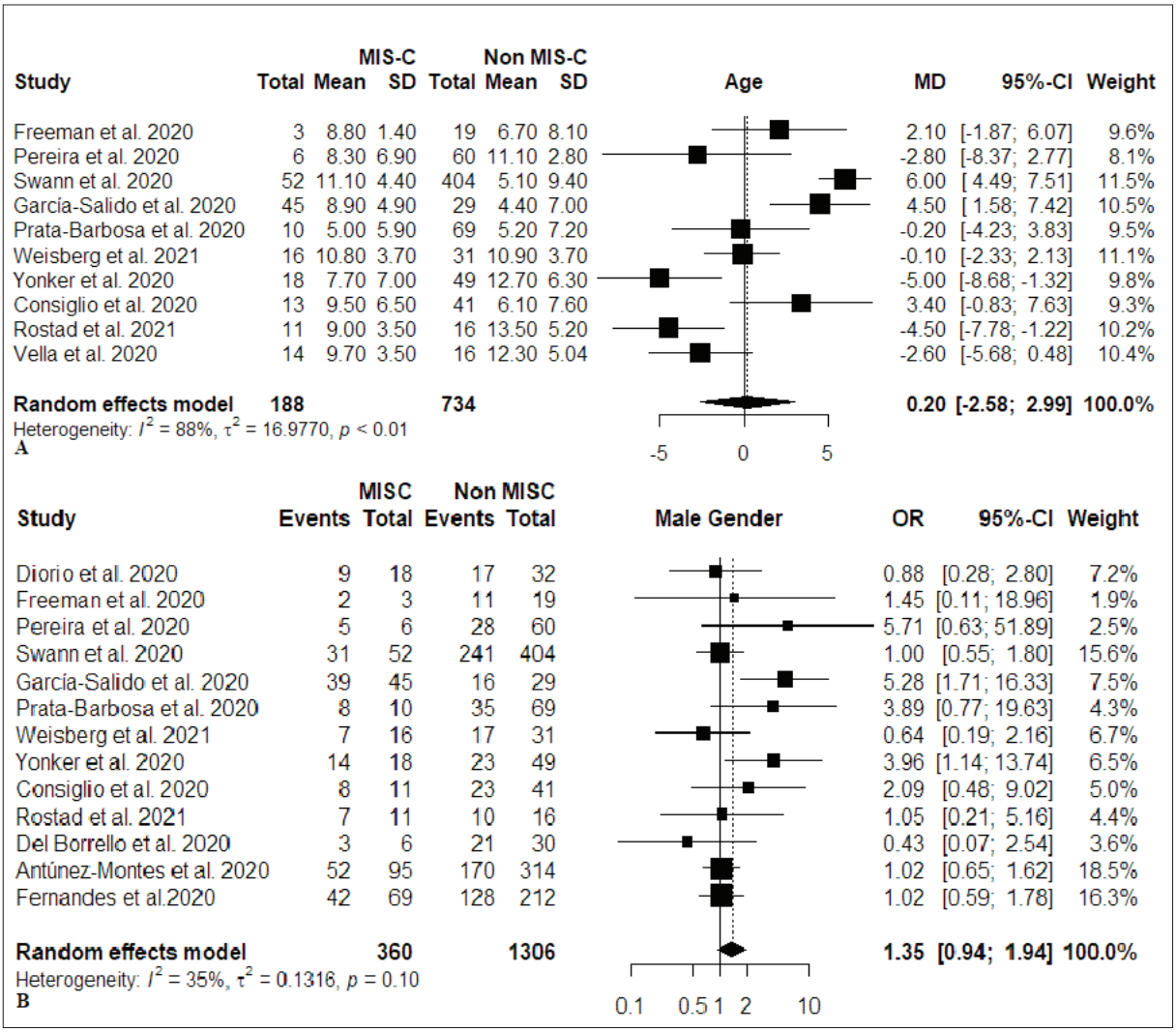

Figure 2. Forest plot of the age mean differences(A) and gender(B) ratio with the MIS-C group vs. non-MIS-C.

value differences were compared, CRP value of MIS-C patients was 11.83 mg/L (95% CI= 2.34; 21.32, I^2= 88.4%, p= 0.015) and ferritin value was 549.22 ng/mL (95% CI= 311.07;787.37, p< 0.001, I^2= 42.0%) and both were statistically significantly higher than that of the non-MIS-C group (Figure 7).

Although mean D-dimer of MIS-C patients was 216.1 ng/mL, higher than the non-MIS-C group, it was not found to be statistically significant.

Cardiac Complications and Radiological Findings

There was a significant increased risk of cardiac complication in MIS-C patients (OR= 18.46, 95% CI= 7.30-46.71, p< 0.001, I^2= 11.3%) (Figure 8).

There was no difference between the groups in terms of the presence of pathology in chest radiography.

Medical Therapy

The possibility of using steroid therapy (OR= 7.09, 95% CI= 3.29-15.26), p< 0.001), IVIG therapy (OR= 55.52, 95% CI= 29.33-105.1, p< 0.001) and inotropic therapy (OR= 12.32, 95% CI= 4.3-34.9), p< 0.001) was higher in the MIS-C group than in the non-MIS-C group (Figures 9,10).

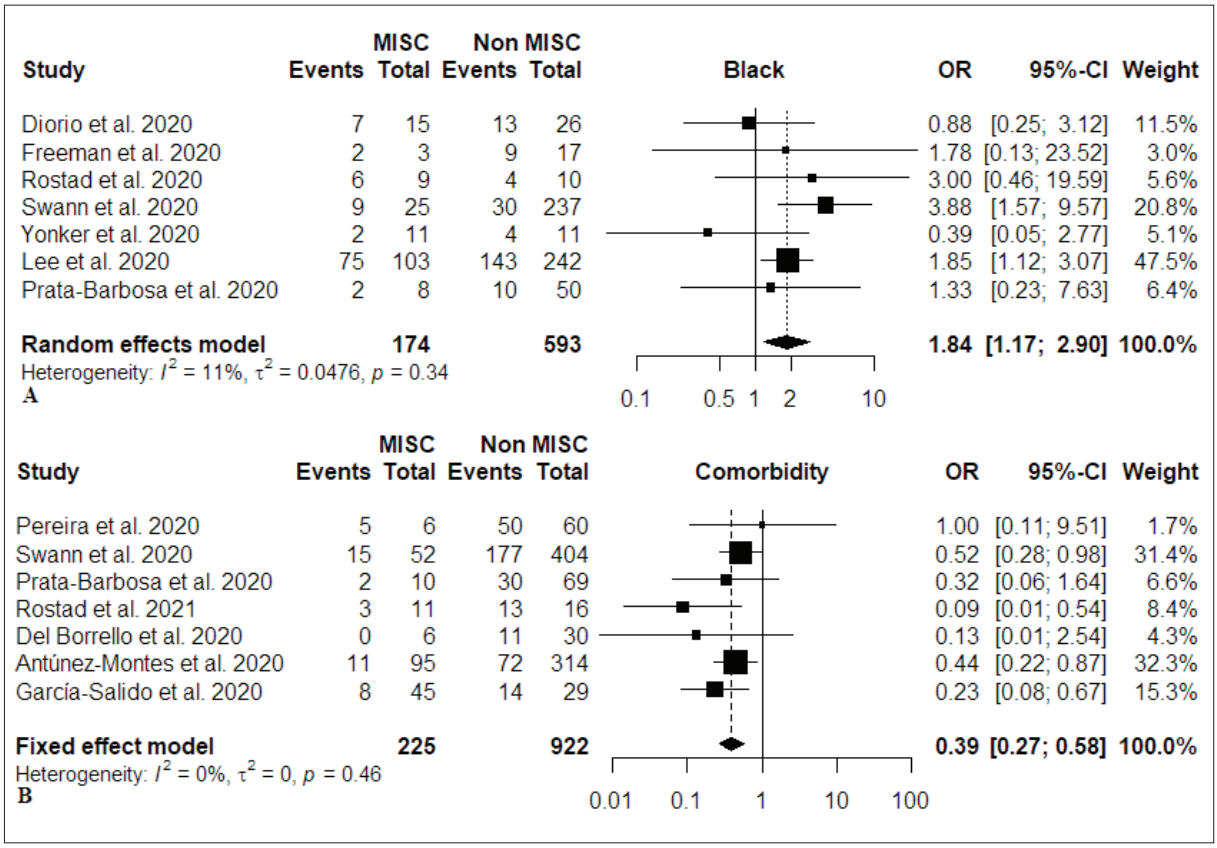

Figure 3. Forest plot of the race **(A)**, comorbidity **(B)** ratio with the MIS-C group vs. non-MIS-C.

There were non-significant differences between the groups with respect to antibiotic therapy and remdesivir.

Intensive Care Unit (ICU) Admission and Organ Support

The need for ICU was 4.7 times higher in MIS-C patients compared to non-MISC patients. (OR= 4.71, 95 % CI= 2.34-9.45, p< 0.001, I^2=66.8%) (Figure 10).

With high heterogeneity between studies, despite the increased need for mechanical ventilation (MV), it did not significantly differ between the MIS-C and non-MIS-C patients.

Non-invasive MV need in MIS-C patients, when compared to non-MIS-C patients, was not statistically significant (OR= 1.50, 95% CI= 0.30-7.58, p= 0.625, I^2= 80%).

Outcome

When evaluated in terms of survival for the outcome status of the study groups, there were non-significant differences between the groups with respect to death (OR= 1.37, 95% CI= 0.23-8.23, p= 0.110, I^2= 66.3%).

Meta-analysis of the sociodemographic, clinical findings and laboratory variables as well as publication bias results are summarized in Table 2 and Table 3.

DISCUSSION

According to the important results of the study, in addition to a difference in race and comorbidity in MIS-C cases, fever, gastrointestinal and dermatological symptoms, and cardiovascular complications were higher as clinical findings. While hematological values were lower, inflammatory markers were found to be higher. The use of steroids, inotropic agents, IVIG and the need for ICU was significantly higher in the treatment of MIS-C patients.

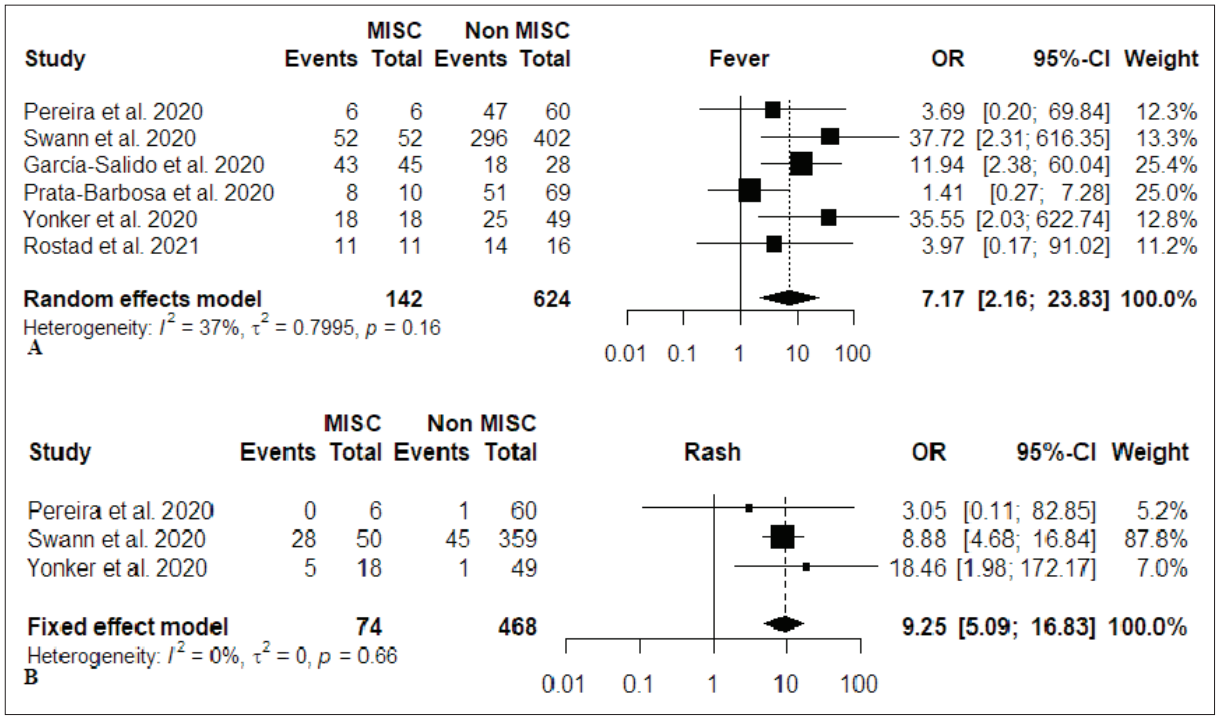

Figure 4. Forest plot of fever **(A)**, rash **(B)**, symptoms ratio with the MIS-C group vs. non-MIS-C.

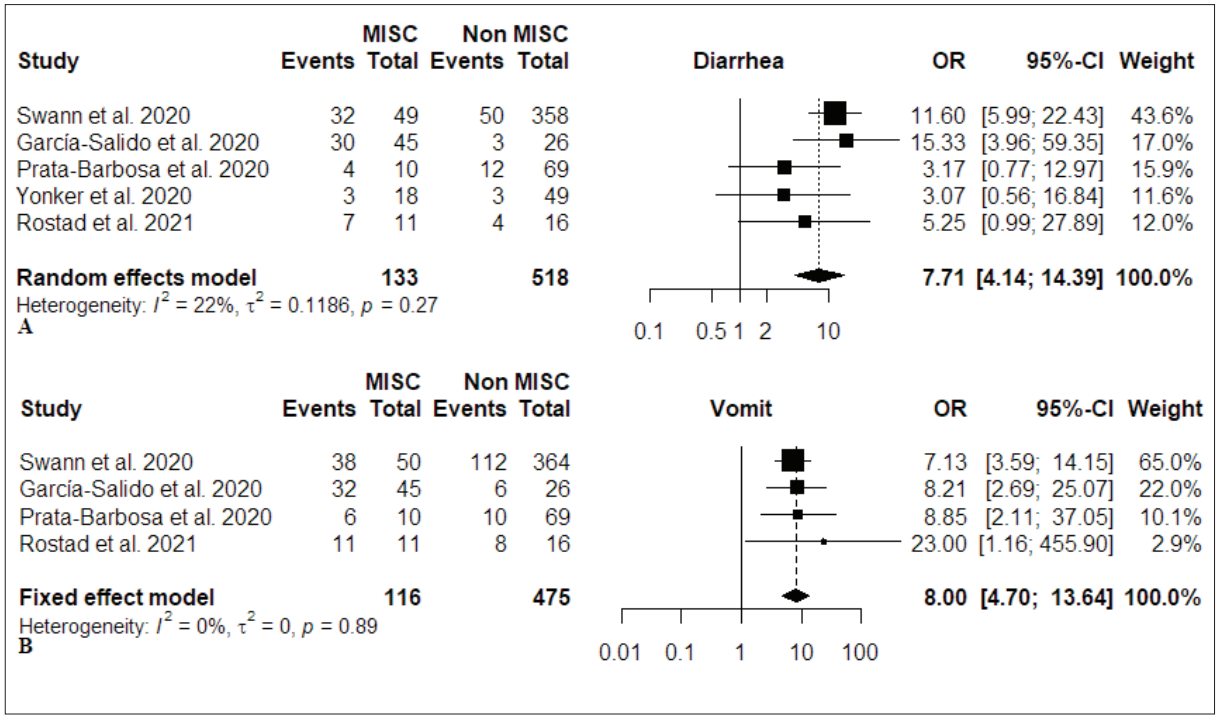

Figure 5. Forest plot of diarrhea(A), vomit(B) symptoms ratio with the MIS-C group vs. non-MIS-C.

Table 2. Meta-analysis of the sociodemographic, clinical and treatment features of MIS-C and Non-MIS-C patients

			Outcomes		
Variables	**Study Number**	**Egger test (p)**	**Model, OR/MD (95% CI)**	**p**	**Heterogeneity P/I^2**
Demographic features					
Age	10	0.042	REM 0.20(-2.58;2.99)	0.886	<0.001/88.0%
Sex	13	0.152	REM 1.35 (0.94-1.94)	0.108	0.102/35%
Black	8	0.652	**REM 1.84 (1.17-2.9)**	**0.002**	**0.343/11.4%**
Hispanic	4	0.434	**FEM 0.5 (0.31-0.8)**	**0.004**	**0.449/0%**
Comorbidity					
Comorbidity	7	0.234	**FEM 0.39 (0.27-0.58)**	**<0.001**	**0.457/0%**
Asthma	4	0.361	REM 1.58(0.72-3.49)	0.257	0.379/2%
Obesity	6	0.890	REM 1.02 (0.29-3.62)	0.972	<0.001/ 76.2%
BMI	3	0.918	REM 1.86(-11.61;15.34)	0.787	<0.001/92.1%
Symptoms					
Fever	6	0.462	**REM 7.17(2.16-23.83)**	**0.001**	**0.161/ 36.7%**
Cough	6	0.719	REM 0.55(0.24-1.26)	0.157	0.017/ 63.5%
Dyspnea	5	0.495	REM 0.53 (0.14-2.04)	0.356	0.0004/80.3%
Rhinorrhea	5	0.776	**FEM 0.17(0.07-0.42)**	**<0.001**	**0.469/0%**
Rash	3	0.439	**FEM 9.25(5.09-16.83)**	**<0.001**	**0.0664/ 0%**
Myalgia	4	0.898	REM 2.53(0.20-31.61)	0.472	<0.001/86.3%
GIS symptoms	3	0.078	**FEM 4.07(2.55-6.49)**	**<0.001**	**0.536/0%**
Vomit	4	0.187	**REM 8.00(4.70-13.64)**	**<0.001**	**0.894/0%**
Diarrhea	5	0.020	**REM 7.71(4.14-14.39)**	**<0.001**	**0.271/22.5%**
Refusal eat	3	0.929	**FEM 2.66(1.22-5.75)**	**0.0139**	**0.410/0%**
Fatigue	4	0.782	**FEM 3.02(1.86-4.90)**	**<0.001**	**0.620/0%**
Headache	6	0.332	REM 0.98 (0.30-3.23)	0.972	<0.001/80.9%
Seizure	3	0.145	REM 2.82(0.10-83.41)	0.549	0.028/71.9%
Cardiac complications					
Cardiac complication	5	0.634	**REM 18.46 (7.3-46.71)**	**<0.001**	**0.341/11.3%**
Radiology findings					
Patology of chest X-ray	5	0.804	REM 0.71 (0.17-3.01)	0.639	< 0.001/83.9%
Medical Therapy					
Antibiotic therapy	4	0.108	REM 1.64 (0.61-4.38)	0.327	0.125/47.7%
Remdesivir	5	0.904	REM 0.51 (0.21-1.22)	0.129	0.383/4.1%
Steroid therapy	10	0.299	**REM 7.09 (3.29-15.26)**	**<0.001**	**< 0.001 /74%**
IVIG therapy	8	0.319	**FEM 55.5 (29.3-105.1)**	**<0.001**	**0.461/0%**
Inotropic therapy	7	0.245	**REM 12.32 (4.34-34.9)**	**<0.001**	**<0.001/76.8%**
ICU admission					
ICU admission	8	0.784	**REM 4.71(2.34-9.45)**	**<0.001**	**0.003/ 66.8%**
Organ support					
Mechanical ventilation	8	0.955	REM 1.43 (0.48- 4.22)	0.519	<0.001/82%
Noninvasive MV	5	0.272	REM 1.50 (0.30- 7.58)	0.625	<0.001/80.4%
Outcome					
Death	6	0.914	REM 1.37 (0.23-8.23)	0.734	0.011/ 66.3%

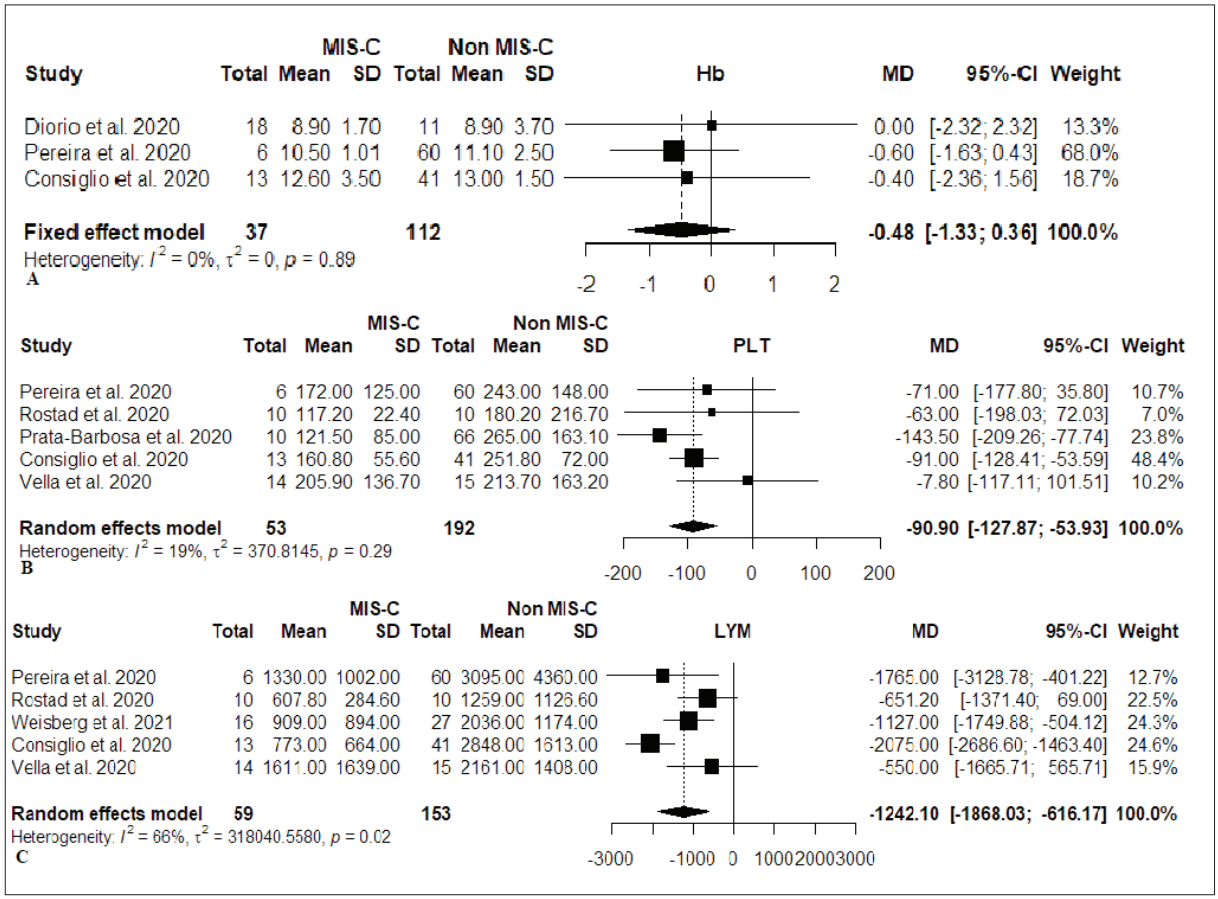

Figure 6. Forest plot graph of the mean difference of hemoglobin(A), platelet(B), lymphocyte(C) in MIS-C and non-MIS-C patients.

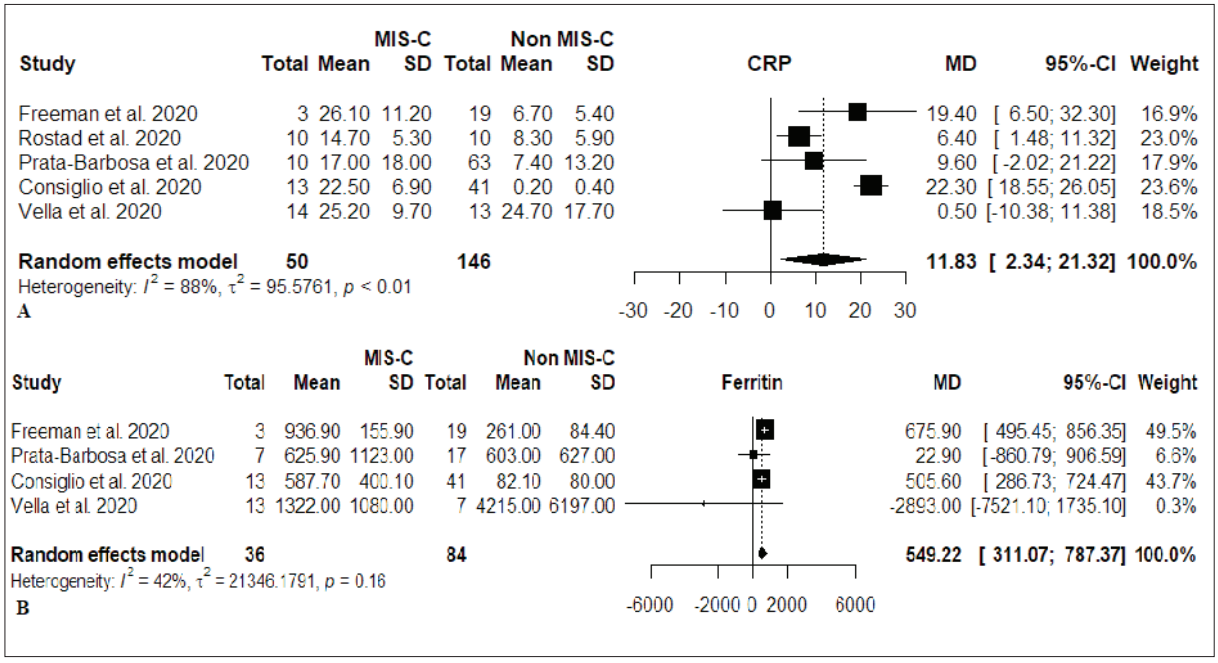

Figure 7. Forest plot graph of the mean difference of CRP(A) and ferritin(B) in MIS-C and non-MIS-C patients.

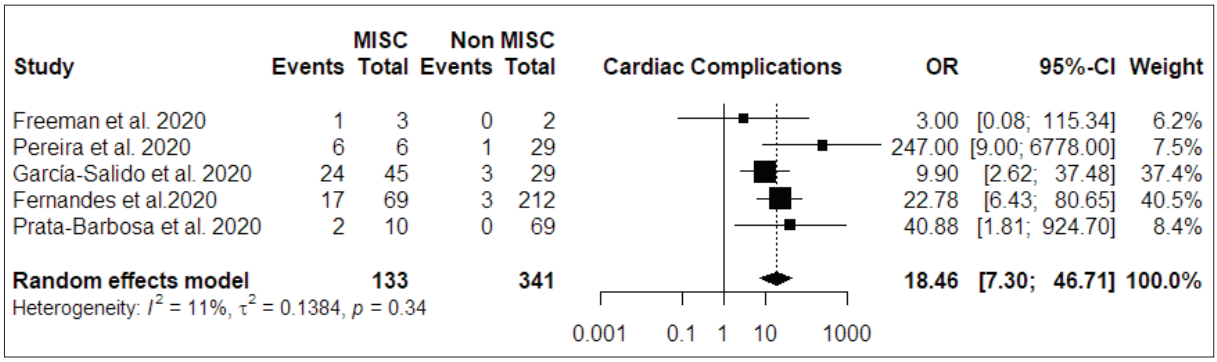

Figure 8. Forest plot of cardiac complications ratio with the MIS-C group vs. non-MIS-C.

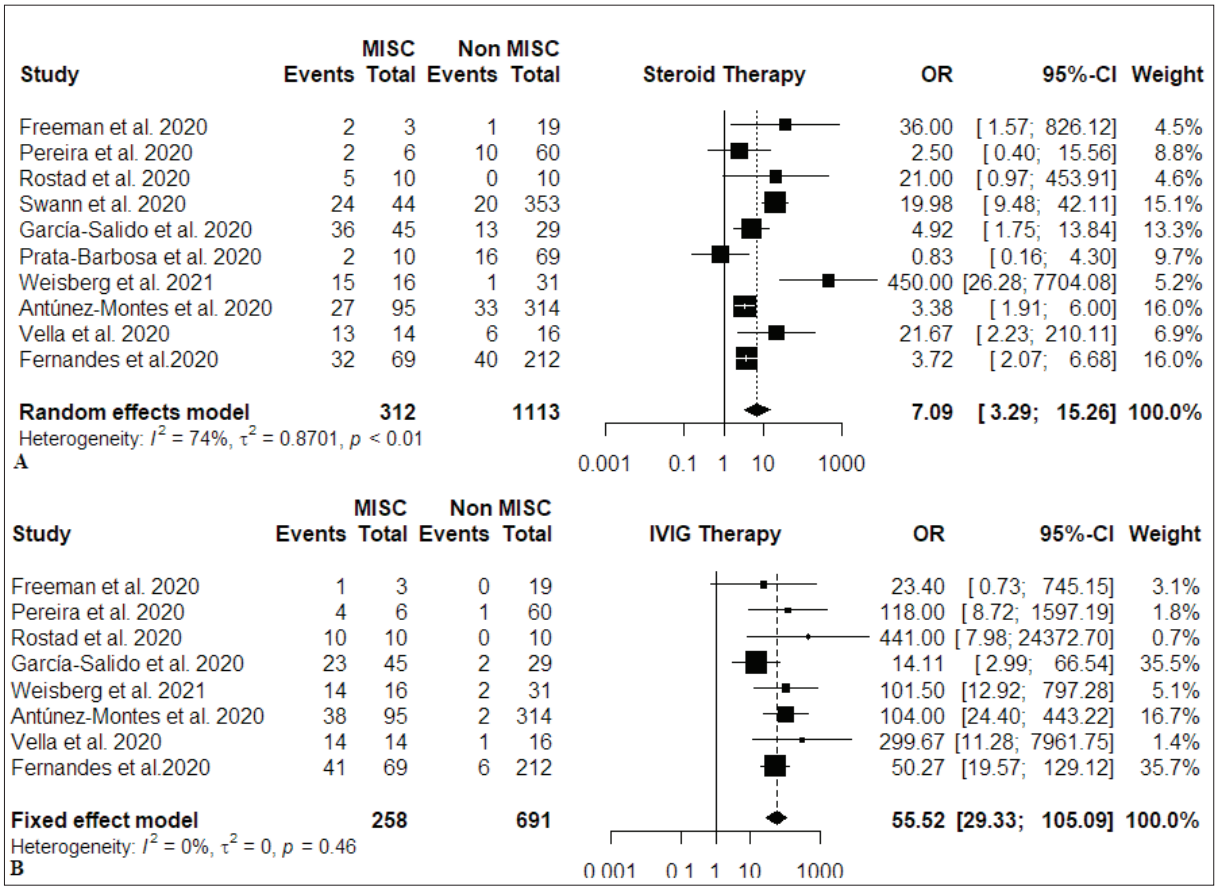

Figure 9. Forest plot graph comparing MIS-C, non-MIS-C patients with use of steroid **(A)**, IVIG **(B)**.

Demographic Features

MIS-C is most common in children between the ages of 1 and 14, and median age is 9[33]. While, in a study comparing severe COVID-19 and MIS-C cases, it has been found that MIS-C patients were concentrated in the 6-12 age group, in another study comparing mean age, no relationship has been found between age and MIS-C development[34,35]. In our study, no difference was found between groups in terms of age.

Male sex is an important risk factor for hospitalization and death in the COVID-19 outbreak[36]. Although studies have reported a

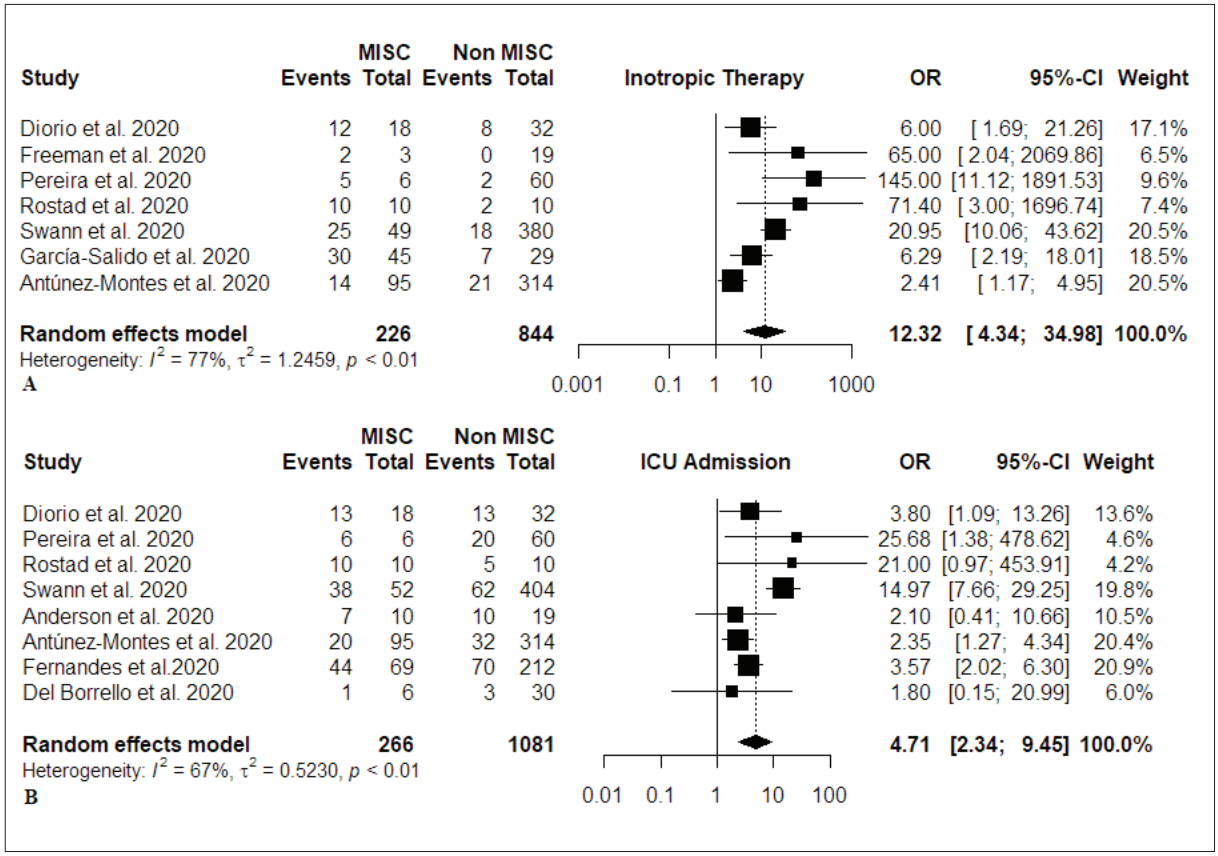

Figure 10. Forest plot graph comparing MIS-C, non-MIS-C patients with use of inotropic therapy **(A)** and need for ICU **(B).**

higher prevalence of MIS-C in males, no clear difference was found between groups in terms of gender in this study[37]. Similar results were obtained in some other studies[34,35].

In this study, white race was taken as reference, being black posed a greater risk for MIS-C, while odds of having hispanic ethnicity was found to be less in MIS-C. Race and ethnicity can be regarded as a determinant of the general health status and socioeconomic level, as well as constituting a genetic trait[38]. It is not clear whether the resulting relationships are a result of genetic traits or access to health care.

Comorbidities

Diseases such as obesity, asthma and cancer are the main health problems that can cause COVID-19 to present as a severe condition[39]. Therefore, it is known that the presence of comorbidity is high in severe COVID-19 cases. Studies have reported that having any comorbidity is less in MIS-C patients[34,35]. This suggests that MIS-C occurs independently of both the severity of COVID-19 and the underlying health problems.

Obesity, the most common comorbidity in pediatric COVID-19 cases requiring hospitalization, is also a risk factor for MV[40-41]. One of the most common comorbidities accompanying COVID-19 is asthma. While the CDC has found the prevalence of chronic lung disease including asthma as 11.6% in pediatric COVID-19 patients, different studies have found the prevalence of asthma between 10.7-15.2% in MIS-C patients[42-46]. In our study, no difference was found between the groups in terms of obesity and asthma frequency.

Symptoms

As a result of the meta-analysis, fever, rash, vomiting, and diarrhea were more common in MIS-C cases, while rhinorrhea was less common on the contrary. MIS-C is not a disease, but a

Table 3. Meta-analysis of the Laboratory Features of MIS-C and Non-MIS-C Patients

Variables	Study Number	Egger test (p)	Outcomes		
			Model, MD (95% CI)	p	Heterogeneity P/I^2
Hematology					
Hb (g/dL)	3	0.848	**FEM -0.75 (-1.48; -0.02)**	**0.045**	**0.774/0%**
WBC (count/mcL)	5	0.968	REM 792.69 (-2990.58;4575.96)	0.681	0.010/70.1%
LYM (count/mcL)	5	0.705	**REM -1242.10 (-1868.03;-616.17)**	**<0.001**	**0.019/66.0%**
PLT (count/mcL)	5	0.509	**REM -90.90 (-127.87;-53.93)**	**<0.001**	**0.291/19.4%**
Inflammatory Markers					
CRP (mg/L)	5	0.446	**REM 11.83 2.34;21.32)**	**0.015**	**<0.001/88.4%**
Ferritin (ng/mL)	4	0.093	**REM 549.22 (311.07;787.37)**	**<0.001**	**0.160/42%**
Coagulation					
D-dimer (ng/mL)	3	0.481	REM 216.08 (-2147.34;2579.50)	0.857	0.054/65.8%

REM: Random effect model, FEM: Fixed effect model.

syndrome with a group of signs and symptoms depending on which body part it affects. Generally, symptoms such as fever, vomiting, diarrhea, skin rash, and fatigue are seen[47]. Many studies have reported fever in almost all cases[35,48]. Rhinorrhea, on the other hand, is a symptom found at a low rate in pediatric COVID-19 cases, and in our study, it was found to be even lower in MIS-C cases[49]. As in our study, high rates of vomiting and diarrhea have been shown in many studies[10,50,51]. In other studies, the most common symptoms have been found as gastrointestinal symptoms like vomiting, abdominal pain, diarrhea, while myalgia and rash are also significant, and headache is partly observed[35,52]. In several systematic review studies, gastrointestinal symptoms have been estimated between 71% and 80%, rash frequency between 42% and 60%, and cough and respiratory symptoms are low in MIS-C cases[53,54]. In a systematic review and meta-analysis, the presence of GIS symptom has been found to be the most common symptom after fever[55]. In our study, the symptoms of refusal eating and fatigue were more common in the MIS-C group. Refusal eating was found to be 11% in a study conducted in the MIS-C group, while it was reported to be 1.7% in a study in children with COVID-19[56,57]. While the prevalence of fatigue symptoms in children with COVID-19 has been reported to be 5-8%, in one study, the prevalence of fatigue in the MIS-C group has been found to be 13.4%[56,58]. Although some studies have shown that MIS-C patients present with epileptic seizures as the first symptom, or MIS-C patients present with any neurological symptom more frequently, the frequency of seizures in MIS-C patients did not differ in our study[59,60].

Laboratory Findings

While SARS-CoV-2 causes serum iron and hemoglobin deficiency, it can mimic the effect of hepcidin and the resulting hyperferritinemia can accelerate the immune response. According to a meta-analysis result, severe COVID-19 patients have more anemia than those with mild symptoms[61]. In another systematic review, hemoglobin value has been found to be lower in MIS-C patients[56]. Consistent with this, Hb was lower in MIS-C patients in our study.

There are studies on the elevation of inflammatory markers in MIS-C, which is a result

of the immune system response being severe or incompatible[35,42,]. In our study, no difference was found between the groups in terms of WBC. Platelet and lymphocyte levels were found to be lower in the MIS-C. In a meta-analysis, WBC has been found to be similar between the groups, while platelet levels have been found to be lower in MIS-C patients. Lymphocyte level was lower in MIS-C patients compared to the mild COVID-19 group, but it was found to be similar to the severe COVID-19 group[62]. In our study, MIS-C patients had higher CRP and ferritin levels. In a meta-analysis, there was no difference in ferritin level between the groups. CRP level was higher in MIS-C patients compared to the mild COVID-19 group, but similar to the severe COVID-19 group[62].

SARS-CoV-2 binds to the endothelial cell via spike protein envelope and angiotensin-converting enzyme-2 located in the cellular membrane of the endothelial cell. It is later suggested to cause increased expression of the platelet tissue factor. Tissue factor is thought to interact with factor VII in the coagulation cascade and ultimately results in thrombin and fibrin production. However, the exact mechanism leading to coagulation changes has not been fully elucidated[63]. Thrombotic events are also seen in MIS-C patients. In many studies, D-dimer level, which is prognostic in thrombotic events, has been found to be higher in the MIS-C group[35,56]. In our study, there was no statistically significant difference between the groups in terms of D-dimer level. In another meta-analysis, D-dimer level was higher in MIS-C patients compared to the mild COVID-19 group, but similar to the severe COVID-19 group[62]. In our study, the group of hospitalized patients with severe and milder COVID-19 comparison with MIS-C patients may have an impact on the result.

Cardiac Complications and Radiological Findings

Coronary artery aneurysm, myocarditis, myocardial dysfunction and similar cardiovascular involvement are more common in MIS-C cases[59]. Consistent with this, we found that cardiac complications were more frequent in cases of MIS-C. This is one of the most obvious differences between MIS-C and non MIS-C patterns, although the mechanism is not yet fully explained.

Chest radiography findings are included in WHO's COVID-19 and RCPCH's MIS-C case definition[8,64]. In this study, no difference was found between the groups in terms of having abnormal chest radiograph findings.

Medical Treatment

In our study, it was found that the use of systemic corticosteroids, IVIG and inotropic drug therapy was higher in the MIS-C group. Corticosteroids and IVIG are among the main drugs used as immunomodulators in the treatment of MIS-C patients, and similar studies have shown that they are used more in the MIS-C group[7,35]. It has been reported that acute cardiac decompensation caused by a severe inflammatory response in the MIS-C group can be seen widely and the need for inotropes can reach 80%[65].

No statistically significant difference was found between the groups in terms of antibiotic and remdesivir use. Although there is no clear opinion about the use of antibiotics in the MIS-C group, antibiotics can be used in the treatment of possible sepsis while the culture results are awaited[7,66]. Remdesivir has been reported to be safe and effective for the treatment of COVID-19 in children[67]. It actively inhibits the replicating virus but most children with MIS-C are not in the acute phase. Therefore, the role of remdesivir in MIS-C treatment is limited[68].

ICU Admission Needs and Organ Support

The need for intensive care was higher in the MIS-C group. Different studies have shown that the need for intensive care is higher in the MIS-C group[56,57]. It has been reported that MIS-C patients often need cardiac or respiratory support, and their intensive care needs range from 44-100%[69].

In our study, no statistically significant difference was found between the groups in terms of MV and non-invasive MV need. Although similar values can be found in studies comparing the need for respiratory support of the severe

COVID-19 and the MIS-C group, there are also studies in which the need was found to be high in the MIS-C group[34,56,57]. MIS-C is a more severe picture that occurs with multiple system involvement after COVID-19 infection[7].

Outcome

According to CDC data, MIS-C fatality rate in the USA is 1.13% (36/3185) as of March 29, 2021, and in another study, MIS-C fatality rate has been found to be 1.5%[53,33]. The risk of death has been found to be 1.9(1.0-2.8) times higher[59]. In our study, although death seemed higher in the MIS-C group, it was not statistically significant. The absence of a difference may have been due to the inclusion of relatively new studies, including advances in treatment and experience gained. In addition, the relatively severe cases of COVID-19 hospitalized by some of our comparison group also affects this result.

Limitations

Our study has some limitations. The most important of these limitations is that the selected studies were comparative observational analytical studies, and there were no experimental studies on treatments and other applications. Many studies have small samples and the fact that there were studies with small samples increases the heterogeneity by decreasing the statistical power. The Egger test showed us that there were problems with publication bias and should be interpreted more carefully when interpreting the result. Since most of the variables examined were not included in every study, the number of studies included in the analysis was less. Since the studies conducted at the same health center that we included at the same time may include the same participants, only one study from the same hospital was analyzed. In some studies, the COVID-19 group (mild, severe or respiratory) has been evaluated as different groups. Although values representing all COVID-19 subgroups were obtained in categorical variables, it was not possible for continuous variables. This situation prevented the analysis of some studies on continuous variables and caused less studies to be included. Another limitation of our study is that we only chose English studies as language.

CONCLUSION

This meta-analysis is the comprehensive study comparing MIS-C and non-MIS-C in terms of demographic, clinical, laboratory, radiological, treatment management and outcome. There was no difference in age and gender between the groups. Black race, fever, rash, diarrhea, vomit, refusal eating and fatigue symptoms, inflammatory markers (CRP, ferritin), cardiac complications, medical treatment use and intensive care need are higher in MIS-C patients. In the non-MIS-C group, the presence of Hispanic ethnicity, comorbidity and hematological values (hemoglobin, lymphocyte, platelet) are higher. There was no difference in terms of obesity status, presence of asthma and death. These results will guide clinicians in the diagnosis of MIS-C. In the coming period, it will be appropriate to conduct a new meta-analysis with studies with larger sample size, longer follow-up time and experimental structure.

ETHICS COMMITTEE APPROVAL

As this study is a meta-analysis, the ethical approval is not necessary.

CONFLICT of INTEREST

No conflicts of interest to be declared concerning the publication of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: CB, MC, SA

Data Collection or Processing: CB, SA, SG, CO, TB, EB

Analysis/Interpretation: CB, SA, SG

Literature Search: All authors

Writing: All authors

Final Approval: CB, MC, SA

REFERENCES

1. *World Health Organization (WHO). Coronavirus disease (COVID-19): Schools. Accessed April 12, 2021. Available on: https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-schools*
2. *American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. Available on: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ (Accessed April 12, 2021).*

3. *Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020;145(6):20200702. https://doi.org/10.1542/peds.2020-0702*
4. *Riphagen S, Gomez X, Gonzalez Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607-8. https://doi.org/10.1016/S0140-6736(20)31094-1*
5. *DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe coronavirus disease-2019 in children and young adults in the Washington, DC, metropolitan region. J Pediatr 2020;223:199-203.e1. https://doi.org/10.1016/j.jpeds.2020.05.007*
6. *World Health Organization (WHO). Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Available on: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 (Accessed April 12 2021).*
7. *Centers for Disease Control and Prevention (CDC). Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) | CDC. Available on: https://www.cdc.gov/mis-c/hcp/index.html (Accessed April 12 2021).*
8. *Royal College of Pediatrics and Child Health (RCPCH). Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available on: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem- inflammatory syndrome-20200501.pdf (Accessed April 12 2021).*
9. *Feldstein LR, Rose EB, Horwitz SM, Collins JP, Margaret M, Newhams MPH, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383(4):334-46. https://doi.org/10.1056/NEJMoa2021680*
10. *Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem ınflammatory syndrome in children in New York state. N Engl J Med 2020;383(4):347-58. https://doi.org/10.1056/NEJMoa2021756*
11. *Diorio C, McNerney KO, Lambert M, Paessler M, Anderson EM, Henrickson SE et al. Evidence of thrombotic microangiopathy in children with SARS-CoV-2 across the spectrum of clinical presentations. Blood Adv 2020;4(23):6051-63. https://doi.org/10.1182/bloodadvances.2020003471*
12. *Anderson EM, Diorio C, Goodwin EC, McNerney KO, Weirick ME, Gouma S, et al. SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19. medRxiv [Preprint] 2020 Aug 18:2020.08.17.20176552. https://doi.org/10.1101/2020.08.17.20176552*
13. *Del Borrello G, Giraudo I, Bondone C, Denina M, Garazzino S, Linari C, et al. SARS-COV-2-associated coagulopathy and thromboembolism prophylaxis in children: A single-center observational study. J Thromb Haemost 2021;19(2):522-30. https://doi.org/10.1111/jth.15216*
14. *Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, et al. Severe acute respiratory syndrome coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr 2021;230(9):23-31.e10. https://doi.org/10.1016/j.jpeds.2020.11.016*
15. *Vella LA, Giles JR, Baxter AE, Oldridge DA, Diorio C, Kuri Cervantes L, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. Sci Immunol 2021;6(57). https://doi.org/10.1101/2020.09.25.20201863*
16. *Rostad BS, Shah JH, Rostad CA, et al. Chest radiograph features of multisystem inflammatory syndrome in children (MIS-C) compared to pediatric COVID-19. Pediatr Radiol 2021;51(2):231-8. https://doi.org/10.1007/s00247-020-04921-9*
17. *Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 Serology in children with multisystem ınflammatory syndrome (MIS-C). Pediatrics 2020;146(6):e2020018242. https://doi.org/10.1542/peds.2020-018242*
18. *Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27(6):1785-805. https://doi.org/10.1177/0962280216669183*
19. *Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14(1):1-13. https://doi.org/10.1186/1471-2288-14-135*
20. *Wells G, Shea B, Robertson J, Welch V, Losos M, Tugwell P, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis.*
21. *CRAN-Package meta. General Package for Meta-Analysis Accessed. Available on: https://cran.r-project.org/web/packages/meta/index.html (Accessed April 12 2021).*
22. *Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34. https://doi.org/10.1136/bmj.315.7109.629*
23. *Antúnez Montes OY, Escamilla MI, Figueroa Uribe AF, Arteaga Menchaca E, Lavariega Saráchaga M, Salcedo Lozada P, et al. COVID-19 and Multisystem inflammatory syndrome in Latin American Children: A multinational study. Pediatr Infect Dis J 2020;40(1):1-6. https://doi.org/10.1097/INF.0000000000002949*
24. *Freeman MC, Gaietto K, DiCicco LA, Rauenswinter S, Squire JR, Aldewereld Z, et al. A comprehensive clinical description of pediatric SARS-CoV-2 infection in Western Pennsylvania. medRxiv [Preprint] 2020;16:2020.12.14.20248192. https://doi.org/10.1101/2020.12.14.20248192*
25. *Pereira MFB, Litvinov N, Farhat SCL, Eisencraft AP, Gibelli MABC, Carvalho WB, et al. Severe clinical spectrum with high mortality in pediatric patients with covid-19 and multisystem inflammatory syndrome. Clinics 2020;75:1-7. https://doi.org/10.6061/clinics/2020/e2209*

26. *Swann O V., 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. https://doi.org/10.1136/bmj.m3249*

27. *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(1):666. https://doi.org/10.1186/s13054-020-03332-4*

28. *Prata Barbosa A, Lima Setta F, Santos GRD, Lanziotti VS, de Castro REV, de Souza DC, et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. J Pediatr (Rio J) 2020;96(5):582-92. https://doi.org/10.1016/j.jped.2020.07.002*

29. *Weisberg SP, Connors TJ, Zhu Y, Baldwin MR, Lin WH, Wontakal S, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol 2021;22(1):25-31. https://doi.org/10.1038/s41590-020-00826-9*

30. *Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, et al. Pediatric Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. J Pediatr 2020;227:45-52.e5. https://doi.org/10.1016/j.jpeds.2020.08.037*

31. *Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020;183(4):968-81.e7. https://doi.org/10.1016/j.cell.2020.09.016*

32. *Lee EH, Kepler KL, Geevarughese A, Paneth-Pollak R, Dorsinville MS, Ngai S, et al. Race/ethnicity among children with COVID-19-associated multisystem ınflammatory syndrome. JAMA Netw Open 2020;3(11):e2030280. https://doi.org/10.1001/jamanetworkopen.2020.30280*

33. *Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States | CDC. Available from: https://www.cdc.gov/mis-c/cases/index.html (Accessed April 14, 2021).*

34. *Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, et al. Characteristics and outcomes of us children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. J Am Med Assoc 2021;325(11):1074-87. https://doi.org/10.1001/jama.2021.2091*

35. *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(8):3227-37. https://doi.org/10.1007/s10067-021-05631-9*

36. *Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun 2020;11(1):1-10. https://doi.org/10.1038/s41467-020-19741-6*

37. *Brizuela M, Lenzi J, Ulloa Gutiérrez R, Antúnez Montez OY, Aida JAR, del Aguila O, et al. Influence of sex on disease severity in children with COVID-19 and multisystem inflammatory syndrome in Latin America. medRxiv Published online 2021:2021.02.07.21251212. https://doi.org/10.1101/2021.02.07.21251212*

38. *Williams DR, Mohammed SA, Leavell J, Collins C. Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities. Ann N Y Acad Sci 2010;1186(1):69-101. https://doi.org/10.1111/j.1749-6632.2009.05339.x*

39. *Certain Medical Conditions and Risk for Severe COVID-19 Illness | Centers for Disease Control and Prevention (CDC). Available on: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (Accessed April 12 2021).*

40. *Wang Y, Lim H. The global childhood obesity epidemic and the association between socio-economic status and childhood obesity. Int Rev Psychiatry 2012;24(3):176-88. https://doi.org/10.3109/09540261.2012.688195*

41. *Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr 2020;174(10). https://doi.org/10.1001/jamapediatrics.2020.2430*

42. *Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem ınflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): A multi-institutional study from New York City. J Pediatr 2020;224:24-9. https://doi.org/10.1016/j.jpeds.2020.06.045*

43. *Lee PY, Day-Lewis M, Henderson LA, Friedman KG, Lo J, Roberts JE, et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. J Clin Invest 2020;130(11):5942-50. https://doi.org/10.1172/JCI141113*

44. *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. https://doi.org/10.1016/j.jpeds.2020.06.044*

45. *Moraleda C, Serna Pascual M, Soriano Arandes A, Simó S, Epalza C, Santos M, et al. Multi-inflammatory syndrome in children related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Spain. Clin Infect Dis 2020;(Figure 1):1-5.*

46. *Bialek S, Gierke R, Hughes M, McNamara LA, Pilishvili T, Skoff T. Coronavirus disease 2019 in children: Current status - Morbidity and Mortality Weekly Report. Available on: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6914e4-H.pdf 2020;69(14):422-6. https://doi.org/10.15585/mmwr.mm6914e4*

47. *Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr 2021;180(7):2019-34. https://doi.org/10.1007/s00431-021-03993-5*

48. *Blumfield E, Levin TL, Kurian J, Lee EY, Liszewski MC. Imaging findings in multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease (COVID-19). Am J Roentgenol 2021;216(2):507-17. https://doi.org/10.2214/AJR.20.24032*

49. *Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: A systematic review. Pediatr Pulmonol 2020;55(10):2565-75. https://doi.org/10.1002/ppul.24991*

50. *Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Eurosurveillance 2020;25(18):1-4. https://doi.org/10.2807/1560-7917.ES.2020.25.18.2000600*

51. *Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. J Am Med Assoc 2020;324(3):294-6. https://doi.org/10.1001/jama.2020.10374*

52. *Nakra N, Blumberg D, 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 2020;7(7):69. https://doi.org/10.3390/children7070069*

53. *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. https://doi.org/10.1016/j.prrv.2020.08.001*

54. *Baradaran A, Malek A, Moazzen N, Shaye ZA. COVID-19 associated multisystem inflammatory syndrome: A systematic review and meta-analysis. Iran J Allergy, Asthma Immunol 2020;19(6):570-88. https://doi.org/10.18502/ijaai.v19i6.4927*

55. *Sood M, Sharma S, Sood I, Sharma K, Kaushik A. Emerging Evidence on multisystem ınflammatory syndrome in children associated with SARS-CoV-2 Infection: a systematic review with meta-analysis. SN Compr Clin Med 2021;3(1):38-47. https://doi.org/10.1007/s42399-020-00690-6*

56. *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*

57. *Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine. 2020;24:100433. https://doi.org/10.1016/j.eclinm.2020.100433*

58. *Rubens JH, Akindele NP, Tschudy MM, Sick Samuels AC. Acute covid-19 and multisystem inflammatory syndrome in children. BMJ 2021;372:1-6. https://doi.org/10.1136/bmj.n385*

59. *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(5):837-48. https://doi.org/10.1002/ppul.25245*

60. *Shenker J, Trogen B, Schroeder L, Ratner AJ, Kahn P. Multisystem inflammatory syndrome in children associated with status epilepticus. J Pediatr 2020;227(1):300-1. https://doi.org/10.1016/j.jpeds.2020.07.062*

61. *Hariyanto TI, Kurniawan A. Anemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Transfus Apher Sci 2020;59(6):102926. https://doi.org/10.1016/j.transci.2020.102926*

62. *Zhao Y, Yin L, Jenil P, Tang L, Huang Y. The inflammatory markers of multisystem inflammatory syndrome in children (MIS-C) and adolescents associated with COVID-19: A meta-analysis. J Med Virol 2021;93(7):4358-69. https://doi.org/10.1002/jmv.26951*

63. *Gabbai Armelin PR, Salomão B, Brighenti FL. Covid-19 (SARS-CoV-2) infection and thrombotic conditions: A systematic review and meta-analysis. Eur J Clin Invest 2021;51(6):e13559. https://doi.org/10.1111/eci.13559*

64. *World Health Organization (WHO) COVID-19 Case definition. Available on: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2 (Accessed April 14 2021).*

65. *Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem ınflammatory 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*

66. *Başar EZ. Çocuklarda COVID-19'a ikincil gelişen multisistemik inflamatuar sendrom. Acta Med Nicomedia 2021;90:0-5.*

67. *Information for Pediatric Healthcare Providers. Available on: https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html (Accessed April 14 2021).*

68. *Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020;20(11):e276-e288. https://doi.org/10.1016/S1473-3099(20)30651-4*

69. *Rafferty MS, Burrows H, Joseph JP, Leveille J, Nihtianova S, Amirian ES. Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: Current knowledge and implications for public health. J Infect Public Health 2021;14(4):484-94. https://doi.org/10.1016/j.jiph.2021.01.008*

Address for Correspondence/Yazışma Adresi

Dr. Saliha AYDIN

Department of Public Health,
Ankara University Faculty of Medicine
Ankara-Turkey
E-posta: saliha_meva@hotmail.com