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Original Research

# One Virus, Two Diseases: Evaluation of Clinical and Immunological Differences in Covid-19 and Multisystem Inflammatory Syndrome Cases

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## Abstract

**Objectives:** This study aims to uncover early detection markers through the immunological analysis of children diagnosed with multisystem inflammatory syndrome (MIS-C) and coronavirus disease-2019 (COVID-19).

**Methods:** We retrospectively analyzed immunological data from thirty-three MIS-C patients and an equivalent number of patients under the age of 18 with a positive polymerase chain reaction (PCR) test for COVID-19. These individuals were admitted to Ondokuz Mayis University between November 2020 and February 2021. In total, the study group consisted of 66 patients and an additional 10 healthy controls.

**Results:** Lymphopenia, thrombocytopenia, anemia, and neutrophilia, along with elevated levels of ferritin, D-dimer, and C-reactive protein, were more pronounced in MIS-C patients ($p<0.001$). No significant disparities were found in serum IgG, A, M, and E concentrations. Notably, there was an increased proportion of B cells ($p<0.001$), an inversion of the CD4/CD8 ratio, and a marked presence of CD3+CD38+HLA-DR+active T cells ($p=0.009$) in the MIS-C cohort.

**Conclusion:** In the early diagnosis of MIS-C, lymphopenia, increase in B cells, reversal of CD4/CD8 ratio, and demonstration of CD3+CD38+HLA-DR+active T cells may be helpful.

**Keywords:** Child, COVID-19, immunology, multisystem inflammatory syndrome

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Multisystem inflammatory syndrome in children (MIS-C) is an emerging concern, strongly linked to the perilous "severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).[1] This condition is typified by fever, heightened inflammatory markers, and the involvement of multiple organ systems in patients confirmed to have a SARS-CoV-2 connection via polymerase chain reaction (PCR), antigen, or antibody tests.[2,3] Although most children exhibit either no symptoms or mild symptoms of COVID-19, some may develop MIS-C several weeks post-infection, presenting with severe clinical signs. The syndrome is believed to be an immune response, manifesting weeks after initial SARS-CoV-2 infection. Not every child with COVID-19 develops MIS-C. The exact determinants, particularly epigenetic ones, remain elusive. There's a growing consensus that dysfunctions in both the innate and adaptive immune systems may underlie its pathophysiology.[1,4] Indeed, cases of severe COVID-19 have indicated some form of immunodeficiency.[4] MIS-C has been

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associated with significant changes in the immune system, suggesting immune dysregulation. Early identification and treatment are imperative; if tackled promptly with intravenous immunoglobulin (IVIG) and corticosteroids, outcomes are generally favorable. This research seeks to contrast the clinical and laboratory profiles of MIS-C and pediatric COVID-19 and to pinpoint early diagnostic markers through immunological assessment.

## Methods

The present study is a single-center study conducted at Ondokuz Mayis University Hospital. It presents a retrospective evaluation of the data of patients who were followed up after the diagnosis of COVID-19 and MIS-C for 4 months between November 2020 and February 2021. Approval was received for the study from the Ethics Committee of Samsun Provincial Health Directorate (Dated: 26.03.2021, no: 26). Patient data were analyzed retrospectively based on the medical records in the electronic database. A total of 66 patients were included in the study group, 33 patients with COVID-19 (age 0-18 years) and 33 patients with MIS-C (0-18 years old). For control purposes, 10 healthy individuals were included in the study. The diagnosis of COVID-19 was made based on PCR positivity detected in oro/nasopharyngeal swab samples and/or lung imaging. All patients were studied for age, gender, medical history, symptoms, assessment of disease severity, laboratory findings (complete blood count, kidney and liver function, lactate dehydrogenase (LDH), myocardial enzymes, coagulation profile, ferritin, C-reactive protein (CRP), procalcitonin, albumin, INR (International Normalized Ratio), fibrinogen, and D-dimer), immunological tests (Ig G, A, M, E, and lymphocyte subgroups), chest computed tomography (CT) findings and treatments, length of hospital stay, underlying diseases, and allergic diseases. The distribution of lymphocytes and lymphocyte subgroups (CD3 T, CD3CD4, CD3CD8, CD19 B, CD20 B, CD3-CD56, CD3+CD56, HLA-DR, CD3+CD38+HLA-DR+, CD3 HLA-DR, CD4 HLA-DR, CD8HLA-DR, CD3/CD8/TCRgd, CD3CD4CD45RACD31, CD45RA, CD4+CD45RA+, CD8+CD45RA+, CD19+CD27-IgD+, CD19+CD27+, CD19+ CD27+IgD+IgM+, CD19+CD27+IgD-IgM-, CD19+CD38+CD21low in the MIS-C group and COVID-19 in comparison with the group of healthy controls was evaluated.

For the definition of MIS-C, criteria defined by the Centers for Disease Control were used.[3] The treatment administered to these patients included supportive therapy, monitoring of lung, liver, kidney, and heart functions, fever control, antiviral treatments, oxygen therapy, IVIG, immunomodulators, corticosteroid, anticoagulation therapy (low-molecular-weight heparin), and empirical antibiotic therapy. Anakinra was administered to MIS-C patients who did not respond to clinical or laboratory treatment.

## Results

### Characteristics of the Patients

A total of 66 patients comprised the study group: 33 with COVID-19 (aged 0-18 years) and 33 with MIS-C (aged 0-18 years) (Table 1). Among the COVID-19 patients, 60% (n=20) had at least one underlying condition, including Wilson's

**Table 1.** Demografic characteristics of the patients with MIS-C and COVID-19

| | Group | | p |
|---|---|---|---|
| | Covid-19 (n=33) (%) | MIS-C (n=33) (%) | |
| Gender | | | |
| Male | 19 (57.6) | 21 (63.6) | 0.644 |
| Female | 14 (42.4) | 12 (36.4) | |
| Age | 12 age 4 month (1 month- 17 age 10 month) | 9 age 1 month (11 month- 16 age 8 month) | 0.045 |
| COVID-19 disease in the family | | | |
| No | 15 (45.4) | 9 (27.3) | 0.111 |
| Yes | 18 (55.6) | 24 (72.7) | |
| Known covid contact | | | |
| No | 11 (33.3) | 7 (21.2) | 0.282 |
| Yes | 22 (66.7) | 26 (78.8) | |
| Intensive care | | | |
| No | 33 (100) | 29(87.8) | 0.043 |
| Yes | 0 (0) | 4 (12.1) | |

*Mann Whitney U test.

disease, congenital merosin deficiency, mucopolysaccharidosis, epilepsy, diabetes, obesity, post-operative medulloblastoma, congenital heart disease, neurofibromatosis type 1, asthma and allergic diseases, acute lymphocytic leukemia (ALL), chronic ITP, obsessive-compulsive disorder, myelocysia, embryonal rhabdomyosarcoma, and obesity. Similarly, 63% (n=21) of the MIS-C patients had underlying conditions such as autoimmune hepatitis, asthma and allergic diseases, obesity, attention deficit disorder, chronic granulomatous disease, prior Kawasaki disease, liver cyst, heart disease, epilepsy, neuromotor developmental delay, and familial Mediterranean fever.

Asthma and allergy-related diseases were present in 18% (n=6) of the COVID-19 patients and 30% (n=10) of the MIS-C patients. Asthma specifically was diagnosed in 21% (n=7) of the MIS-C patients and 6% (n=2) of the COVID-19 patients. Notably, these findings, although not statistically significant, suggest a higher prevalence of asthma and allergies in the MIS-C group. Obesity was observed in two patients from each group. A child is considered obese if their weight exceeds the 97$^{th}$ percentile for their age and gender.

In the MIS-C cohort, three patients presented with acute/perforated appendicitis, and one patient had acute pancreatitis. Asymptomatic COVID-19 patients without any underlying conditions were monitored as outpatients, so this study only included hospitalized patients. Hospitalization duration differed significantly between the groups (p=0.001): a median of 5 days (ranging from 2-10 days) for COVID-19 patients and 6.5 days (ranging from 3-20 days) for MIS-C patients. The median fever duration for MIS-C patients was 4.5 days, with a range of 2-6 days.

Lung imaging (either radiography or CT) showed signs of ground-glass opacity, local irregular shading, and interstitial abnormalities in 30% (n=10) of COVID-19 patients and 12% (n=4) of MIS-C patients. Coronary artery dilation (n=6), myocarditis (n=4), and endocarditis (n=2) were detected only in MIS-C cases, with no cardiac involvement observed in the COVID-19 cases (p<0.001). Four patients required intensive care; however, no fatalities occurred in either group.

Supportive treatment for COVID-19 patients included favipiravir in 9% (n=3), lopinavir in 9% (n=3), antibiotherapy (either azithromycin or clarithromycin) in 39% (n=13), and hydroxychloroquine in 21% (n=7). For MIS-C cases, 96% received IVIG and prednol, while anakinra and inotropic support were administered to 6% (n=2). Favipiravir and lopinavir were used in 9% (n=3) of the MIS-C cases. All MIS-C patients received empirical broad-spectrum antibiotic therapy pending blood and urine culture results.

Boys were more frequently affected, with 63.6% of MIS-C cases and 57.6% of COVID-19 cases being male. The median age for COVID-19 patients was 12 years and 4 months (ranging from 1 month to 17 years and 10 months), whereas for MIS-C patients, it was 9 years and 1 month (ranging from 11 months to 16 years and 8 months). A family history of COVID-19 or known contact with a COVID-19 patient was more common in the MIS-C group. MIS-C patients had a higher need for intensive care, with 12.1% (n=4) admitted to the intensive care unit.

The primary complaint upon admission for COVID-19 patients was fever (74%). MIS-C patients frequently presented with fever (100%), abdominal pain (72%), vomiting (57%), diarrhea (54%), headache (54%), body rash (51%), and muscle pain (45%). MIS-C patients were less likely to report a sore throat, bad taste, and cough compared to those with COVID-19. Gastrointestinal findings and body rash were significantly different between the two groups (p<0.001) (Table 2).

Differences in laboratory parameters were observed between the MIS-C and COVID-19 groups. Lymphopenia was

**Table 2.** The comparison of clinical findings by MIS-C and COVID-19

| | Group | | | |
|---|---|---|---|---|
| | **Covid-19** | **MIS-C** | **Toplam** | **p** |
| Fever | 23 (74.2) | 32 (97) | 55 (85.9) | 0.012 |
| Cough | 11 (36.7) | 4 (12.1) | 15 (23.8) | 0.047 |
| Diarrhea | 5 (16.7) | 18 (54.5) | 23 (36.5) | 0.004 |
| Vomiting | 3 (10) | 19 (57.6) | 22 (34.9) | 0.001 |
| Abdominalpain | 1 (3) | 24 (72.7) | 25 (37.9) | 0.001 |
| Headache | 4 (13.3) | 18 (54.5) | 22 (34.9) | 0.002 |
| Taste Disorder in the Mouth | 5 (16.7) | 4 (12.1) | 9 (14.3) | 0.725 |
| Rash | 0 (0) | 17 (51.5) | 17 (27) | 0.001 |
| Myalgia | 7 (23.3) | 15 (45.5) | 22 (34.9) | 0.115 |
| Soretroat | 8 (26.7) | 8 (24.2) | 16 (25.4) | 1.000 |
| Neurological Finding | 1 (3.3) | 8 (25.8) | 9 (14.8) | 0.026 |

*Mann Whitney U test.

more prevalent in MIS-C patients, whereas leukocytosis was due to an increased neutrophil count (p=0.001). MIS-C patients also had more pronounced anemia and thrombocytopenia. Furthermore, two inflammatory markers, CRP and ferritin, were significantly higher in the MIS-C group (p<0.001) (Fig. 1). Blood biochemical tests revealed hypoalbuminemia, hyponatremia, and elevated coagulation tests in MIS-C patients compared to those with COVID-19 (p<0.001) (Table 3). There were no significant differences in IgG (p=0.279), IgA (p=0.549), IgM (p=0.876), and IgE (p=0.624) levels between the groups.

Significant differences in leukocyte (p=0.001), neutrophil (p<0.001), platelet (p=0.018), ferritin (p<0.001), eosinophil (p=0.004), and CRP (p<0.001) values were observed between the COVID-19 and MIS-C groups. Additionally, CD3 (p=0.002), CD19 (p<0.001), and activated T cells (p=0.009) displayed significant variations between the groups (Fig. 2). The average lymphocyte percentage was 26.6% for MIS-C patients, compared to 47.3% for healthy controls. In the COVID-19 group, CD19 B cells were significantly lower than in the MIS-C group and healthy controls (p<0.000). Comparing the two patient groups, both exhibited lymphopenia, but it was more pronounced in the MIS-C group (p<0.001). In terms of lymphocyte distribution, CD3 T lymphocytes were even more reduced, and while CD4 T cells and NK cells were significantly decreased, B lymphocytes and CD8 T cells proportionally increased. The T4-to-T8 ratio of 2/1 was disrupted in the MIS-C group. No significant differences were observed in the distributions of other parameters (Table 4).

## Discussion

Clinical and laboratory differences between MIS-C and COVID-19 cases have been observed, with variations in the host's immune responses. This study aimed to identify early detection markers based on the immunological evaluation of children diagnosed with MIS-C and COVID-19.

Infections with SARS-CoV-2 usually result in a mild upper respiratory illness in children. In a study from Turkey encompassing 220 children with COVID-19, 66% of cases were found to be asymptomatic or had a mild disease progression, with 2.7% presenting severe symptoms.[5] Yet, following the disease's peak period, severe clinical instances, attributed to MIS-C, began emerging in children. MIS-C's manifestation, weeks after SARS-CoV-2 infection, is speculated to be an immunological aftermath tied to post-infectious or delayed infectious events. In some patients, while the PCR test from nasal swabs couldn't detect the disease, antibody tests indicated prior infection.[6] Reports from China and other afflicted countries highlighted a hyperinflammatory process in adult patients due to the novel coronavirus, producing clinical and laboratory outcomes

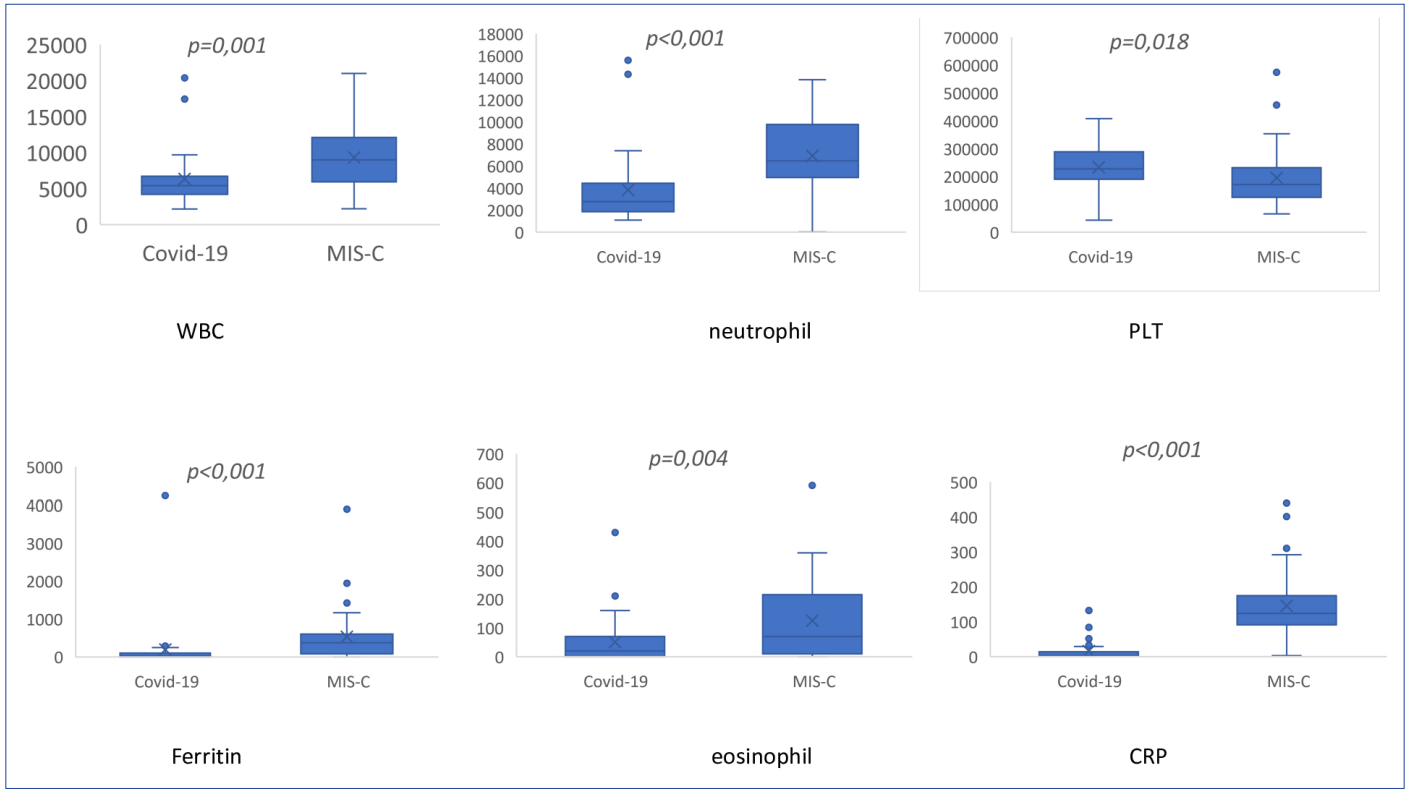


**Figure 1.** Leukocyte, Neutrophil, Platelet, Ferritin, Eosinophil, and CRP Values between COVID-19 and MIS-C Groups.

**Table 3.** The comparison of laboratory by groups

| | Group | | p* |
|---|---|---|---|
| | Covid-19 | MIS-C | |
| Hb | 12.7 (5.9 - 16.8) | 11.4 (8.8 - 13.3) | 0.000 |
| Hct | 36.6 (16,1 - 1430) | 31.3 (26,2 - 40) | 0.000 |
| Wbc | 5400 (2190 - 20360) | 9010 (2220 - 20990) | 0.001 |
| Lymphocyte | 1490 (180 - 5070) | 1070 (280 - 4350) | 0.065 |
| Neutrophil | 2770 (1100 - 15580) | 6470 (17.6 - 13820) | 0.000 |
| Monocyte | 620 (120 - 1410) | 380 (120 - 2520) | 0.164 |
| Basophil | 20 (0 - 70) | 20 (0 - 50) | 0.443 |
| Eosinophil | 20 (0 - 430) | 70 (0 - 590) | 0.004 |
| PLT | 227000 (43000 - 408000) | 171000 (66000 - 574000) | 0,018 |
| Crp | 3 (1 - 132) | 124 (3.1 - 440) | 0.000 |
| Sedimentation | 19 (5 - 215000) | 34 (10 - 160) | 0.134 |
| D Dimer | 319 (84 - 4561) | 4705 (233 - 100000) | 0.000 |
| Cpk | 77 (1.8 - 3741) | 60.5 (21 - 561) | 0.665 |
| Ck-Mb | 1.1 (0.3 – 2.8) | 1.3 (0 – 4.5) | 0.526 |
| Troponın I | 0.1 (0.1 – 0.1) | 0.1 (0.1 – 1.1) | 0.059 |
| Ldh | 264 (0.2 - 479) | 283.5 (135 - 546) | 0.048 |
| Ferritin | 22 (0 - 4237) | 374 (0 - 3896) | 0.000 |
| AST | 26 (10 - 264) | 29 (9 - 1098) | 0.129 |
| ALT | 17 (6 - 555) | 21 (5 - 902) | 0.117 |
| Creatinine | 0.6 (0.3 – 6.4) | 0.5 (0.2 - 1) | 0.011 |
| Sodium | 140 (0.3 - 144) | 135 (38 - 145) | 0.000 |
| Albumin | 4.7 (3.1 – 5.4) | 3.4 (2.2 – 4.8) | 0.000 |
| IgG | 1100 (597 - 1530) | 1175 (657 - 1540) | 0.279 |
| IgA | 117 (18 - 281) | 113 (22 - 280) | 0.549 |
| IgM | 105 (36 - 272) | 113 (9 - 244) | 0.876 |
| IgE | 38,2 (18 - 588) | 34 (17.8 - 614) | 0.624 |

* Mann Whitney U test, median (min-max); Hb: Hemoglobin; Hct: Hematocrit; WBC: White bloodcell; PLT: Platelet; CRP: C reactive protein; CPK: creatine kinase; LDH: lactate dehydrogenase; AST: Aminotransferase test; ALT: Alanineaminotransferase.

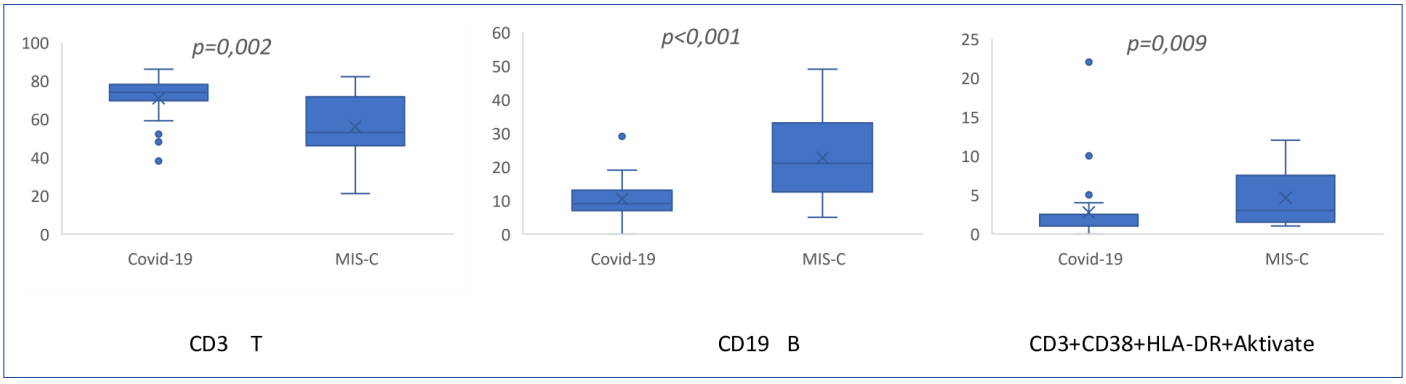


**Figure 2.** CD3, CD19, and Activated T Cells between COVID-19 and MIS-C Groups.

resembling hemophagocytosis.[1] The Kawasaki-like syndrome observed in children is also believed to be a clinical manifestation of this hyperinflammatory response to the virus. The precise cause behind this delayed hyperinflammatory syndrome in children remains unclear.[6] However, initial findings suggest effective patient responses to IVIG and immunosuppressive treatments, paralleling traditional Kawasaki disease. Swift IVIG intervention is crucial as the disease may trigger a cytokine storm.

While the prevalence of laboratory-confirmed COVID-19 in

**Table 4.** Evaluation of lymphocyte subgroups according to groups

| | COVID-19 (Group C) | | MIS-C (Group M) | | Healthy controls | | p |
|---|---|---|---|---|---|---|---|
| | Median± a. deviation | Median (Min-Max) | Median± a. deviation | Median (Min-Max) | Median± a. deviation | Median (Min-Max) | |
| Lymphocyte | 40.8 ± 14.7[b] | 41.0 (10.0 – 72.0) | 26.6 ± 12.4[a] | 24.0 (10.0 – 55.0) | 47.3 ± 14.4[b] | 44.0 (31.0 – 70.0) | 0.0001 |
| CD3 T | 70.8 ± 11.8 | 74.0 (38.0 – 86.0)[a] | 56.0 ± 16.6 | 53.0 (21.0 – 82.0)[b] | 64.5 ± 7.0 | 64.0 (47.0 – 75.0)[ab] | 0.0022 |
| CD3CD4 T4 | 42.1 ± 11.9[b] | 43.0 (17.0 – 65.0) | 31.9 ± 10.3[a] | 31.0 (13.0 – 50.0) | 39.9 ± 7.2[b] | 39.0 (29.0 – 52.0) | 0.0051 |
| CD3CD8 T8 | 28.2 ± 8.4 | 27.0 (12.0 – 48.0) | 23.7 ± 8.0 | 25.0 (8.0 – 39.0) | 24.1 ± 6.1 | 24.0 (15.0 – 35.0) | 0.1141 |
| CD19 B | 10.4 ± 6.0 | 9.0 (0.0 – 29.0)[a] | 22.7 ± 12.3 | 21.0 (5.0 – 49.0)[b] | 17.7 ± 6.8 | 17.0 (2.0 – 28.0)[b] | 0.0002 |
| CD20 B | 10.5 ± 6,1[a] | 10.0 (0.0 – 29.0) | 22.0 ± 13.0[b] | 19.0 (5.0 – 46.0) | 18.7 ± 5.8[b] | 18.0 (12.0 – 31.0) | 0.0001 |
| CD3-CD56 NK | 10.8 ± 8.2 | 9.0 (1.0 – 34.0) | 7.5 ± 5.8 | 5.0 (0.0 – 23.0) | 10.4 ± 6.2 | 8.0 (3.0 – 23.0) | 0.2092 |
| CD3+CD56 NKT | 4.1 ± 3.2 | 4.0 (0.0 – 10.0) | 2.6 ± 3.1 | 1.0 (0.0 – 11.0) | 1.7 ± 2.0 | 1.0 (0.0 – 6.0) | 0.0512 |
| HLA-DR | 23.3 ± 10.5 | 21.0 (13.0 – 53.0)[a] | 34.7 ± 12.6 | 37.5 (13.0 – 56.0)[b] | 25.5 ± 5.0 | 27.0 (18.0 – 34.0)[ab] | 0.0032 |
| CD3+CD38+HLA-DR+ Aktivate T | 2.8 ± 4.5 | 1.0 (0.0 – 22.0)[b] | 4.6 ± 3.5 | 3.0 (1.0 – 12.0)[a] | 1.0 ± 0.7 | 1.0 (0.0 – 3.0)[b] | 0.0002 |
| CD3HLA-DR Omenn panele | 7.2 ± 5.9 | 5.0 (2.0 – 27.0) | 7.1 ± 5.1 | 5.5 (0.0 – 19.0) | 4.2 ± 2.6 | 5.0 (0.0 – 8.0) | 0.2492 |
| CD4HLA-DR Aktivate T4 | 8.2 ± 14.0 | 4.0 (2.0 – 70.0) | 6.2 ± 3.8 | 5.5 (0.0 – 13.0) | 3.9 ± 2.2 | 4.0 (1.0 – 10.0) | 0.1922 |
| CD8HLA-DR Aktivate T8 | 17.6 ± 12.1 | 14.0 (5.0 – 50.0) | 18.1 ± 11.8 | 19.0 (1.0 – 41.0) | 11.5 ± 8.6 | 9.0 (3.0 – 33.0) | 0.1272 |
| CD3/CD8/TCRgd | 21.2 ± 10.6 | 21.0 (5.0 – 48.0) | 17.0 ± 10.0 | 16.0 (3.0 – 37.0) | 21.1 ± 7.3 | 22.0 (10.0 – 32.0) | 0.2821 |
| CD3CD4CD45RACD31 RTE | 44.2 ± 16.4[b] | 48.0 (8.0 – 75.0) | 45.1 ± 14,0[b] | 43.0 (20.0 – 73.0) | 56.3 ± 14.5[a] | 56.0 (29.0 – 75.0) | 0.0421 |
| CD45RA | 62.5 ± 11.8 | 64.0 (43.0 – 91.0)[a] | 65.7 ± 10.9 | 66.0 (45.0 – 85.0)[ab] | 74.1 ± 11.9 | 80.0 (58.0 – 89.0)[b] | 0.0202 |
| CD4+CD45RA+ NaiveT4 | 52.3 ± 20,1 | 50.0 (12.0 – 91.0) | 56.0 ± 14.3 | 53.5 (32.0 – 82.0) | 65.4 ± 13.7 | 67.0 (40.0 – 84.0) | 0.0771 |
| CD8+CD45RA+ NaiveT8 | 47.8 ± 14.9[b] | 47.0 (24.0 – 89.0) | 59.5 ± 19.4[a] | 63.0 (25.0 – 95.0) | 59.4 ± 14.3[a] | 58.0 (33.0 – 79.0) | 0.0321 |
| CD19+CD27-IgD+ Naive | 69.0 ± 18.9 | 72.0 (0.0 – 96.0) | 74.6 ± 15.0 | 78.0 (30.0 – 95.0) | 76.9 ± 12.9 | 77.0 (55.0 – 92.0) | 0.2692 |
| CD19+CD27+ Memory | 20.4 ± 12.7 | 21.5 (0.0 – 53.0) | 19.2 ± 14.5 | 15.0 (3.0 – 61.0) | 17.7 ± 10.5 | 16.0 (6.0 – 40.0) | 0.7942 |
| CD19+ CD27+IgD+IgM+ Nonswıtched | 8.5 ± 6.8 | 7.5 (0.0 – 32.0) | 10.8 ± 11.5 | 7.0 (1.0 – 51.0) | 8.6 ± 5.7 | 6.5 (2.0 – 21.0) | 0.9922 |
| CD19+CD27+IgD-IgM- Swıcthed | 10.3 ± 8.5 | 9.0 (0.0 – 29.0) | 9.2 ± 8.2 | 6.0 (0.0 – 35.0) | 7.9 ± 4.8 | 9.0 (2.0 – 14.0) | 0.8252 |
| CD19+CD38+CD21low | 4.8 ± 3.9 | 5.0 (0.0 – 12.0) | 3.2 ± 6.1 | 1.0 (0.0 – 29.0) | 2.6 ± 1.3 | 2.0 (1.0 – 6.0) | 0.0732 |

[1]One-way analysis of variance test statistic; [2]Kruskal Wallis test statistic, [a-b]: There was no difference between groups.

individuals below 21 years was 322/100,000, MIS-C had an incidence of approximately 2/100,000^7. Most MIS-C patients yielded a negative PCR result for COVID-19 but tested positive through antibody serology, bolstering the theory that MIS-C emerges from immune dysregulation after the initial acute infection phase. However, in some cases, both PCR and antibody tests for COVID-19 can be positive or, less frequently, negative.[7,8] Serological positivity was found in all of our MIS-C cases.

Both the COVID-19 and MIS-C groups predominantly consisted of male patients, consistent with existing literature. MIS-C was more prevalent in younger individuals compared to COVID-19. A significant portion had either a direct family history of COVID-19 or confirmed contact with an infected individual. Nevertheless, some lacked both contact forms. Therefore, regardless of direct family history or known contact, clinical and laboratory diagnostics play a pivotal role. While adults with COVID-19 primarily manifest pulmonary symptoms, pediatric cases tend to be asymptomatic. Relative to adults, both COVID-19 and MIS-C cases in children have heightened gastrointestinal involvements.[9] Fever and gastrointestinal system findings are conspicuous, especially in the MIS-C cases. Our MIS-C cases mostly had fever (97%) and gastrointestinal findings (90%). In the study by Ahmed et al.[8] it was reported that the complaint of abdominal pain was obvious in the cases. Lishman et al.[10] published a case report of "Acute Appendicitis in Multisystem Inflammatory Syndrome in Children with COVID-19". In our study, similar to those in the literature, three cases presented with acute appendicitis and were operated for it. Hence, MIS-C should be kept in mind in the differential diagnosis of patients presenting with gastrointestinal complaints such as abdominal pain, vomiting, and diarrhea.

Cardiac involvement in MIS-C, though not fully elucidated, is believed to be tied to systemic inflammation, acute viral myocarditis, hypoxia, stress cardiomyopathy, and, occasionally, coronary artery ischemia.[9] Although coronary artery dilatation (n=6), myocarditis (n=4), and endocarditis (n=2) were detected during the acute period in the patients diagnosed with MIS-C, none of the patients had cardiac problems during the chronic period.

Lymphopenia and disorders in T and B cells can cause severe disease in the immune system, which might eventually lead to a cytokine storm. In a study with 69 COVID-19 patients and 21 healthy controls, those admitted to the clinic included a total of 69 patients infected with SARS-CoV-2 and were grouped as patients with asymptomatic infection (n=14), non-severe infection (n=39), and severe infection (n=16). Lymphocyte levels decreased in severe COVID-19 patients, and CD4 expression was observed in monocytes of patients with severe COVID-19. Total lymphocytes, B and T lymphocytes, CD4+ cells and CD8+ cells, and NK and NKT cells were found to be decreased in patients with severe COVID-19. The CD4+/CD8+ ratio was significantly different between the COVID-19 patients and the group of healthy controls. In COVID-19, plasma B cells increased while naive B cells decreased. The percentage of activated T cells (CD3+, HLA-DR+) and B cells (CD19+, CD38+) was lower in patients with severe COVID-19.[11,12]

In our study, we observed that total lymphocytes, B cells, and NK cells decreased, while active T cells increased in the COVID-19 group. Conversely, in the MIS-C group, lymphopenia was more pronounced, T cells showed a further decrease, and B cells proportionally increased. Moreover, in the MIS-C group, while the number of helper T cells decreased, cytotoxic T cells increased, reversing the 2:1 ratio typically seen between them. We also noted a decline in NK and NKT cells, but an uptick in active T cells in the MIS-C group. According to published literature, MIS-C is linked with higher levels of HLA-DR+, CD38+, CD4+, and CD8+ T cells than pediatric cases of COVID-19.[13] The same virus appears to exert different effects on the host's immune response.[13] The same virus appears to have different effects on the host immune system.

NK cells are a type of innate lymphoid cells that contribute to the cytolytic killing of virus-infected cells. In the study conducted with COVID-19 patients, NK, and CD3+ CD56+ NKT cells were found to be significantly lower. In addition, while asymptomatic COVID-19 patients had higher NK cells, decreased levels were reported in severe patients.[13] In our patients, NK cells were decreased in both COVID-19 and MIS-C cases although not statistically significant, which is in line with the literature. However, NK and NKT cells decreased more in MIS-C cases. These data suggest that MIS-C is associated with the activation of native lymphocytes in addition to conventional CD4+ and CD8+ T cells.

In a study distinct from ours, patients were assessed during the acute, convalescent, and recovery phases. The characteristics of lymphocyte subgroups were analyzed across all three stages. A parallel finding with our research was evident in the acute phase, where 84% of the children presented with lymphopenia. Decreases in the absolute counts of CD3, CD4, and CD8 cells were observed in 88%, 72%, and 84% of the patients, respectively. Natural killer cells showed a decline in 63% of the patients, and CD19 in 59%. Additionally, this study established a correlation between lymphopenia and hypotension, one of the severe clinical manifestations of the disease.[14]

Although activated T lymphocytes and B lymphocytes seem to be proportionally increased in MIS-C, they may not be functional. It is not yet known whether the active B cells are sufficient or functional or to what extent neutralizing antibodies are synthesized for protection against the virus.

Therefore, patients are quickly administered IVIG. IVIG is a blood product containing polyclonal IgG. Antigen presentation, expression of proinflammatory cytokines, apoptosis, differentiation and maturation of immune cells, antibody-dependent cellular cytotoxicity, phagocytosis, and regulation of T cell population can be achieved because of the interaction of Fc gamma receptors and IgG-Fc found in almost all immune cells.[15] Owing to its immunomodulatory effects, IVIG is also widely used in the treatment of many autoimmune and systemic inflammatory diseases. It has been suggested that IVIG treatment, which is known to have an immunomodulatory effect at high doses, reduces the cytokine storm in COVID-19 patients presenting with severe disease indications. This effect is achieved through clearance of complement, inhibition of innate immune cells, effector T cell activation, and proliferation of T regulatory cells.[16]

As recommended in the guidelines, patients diagnosed with MIS-C in this study were treated with IVIG, steroids, and anticoagulants; however, favipiravir was not administered to all patients. Since the main problem in MIS-C is not an acute viral infection but rather the hyperinflammation triggered by the virus, the goal is to regulate the immune system with steroids and IVIG. All of the follow-up patients exhibited positive responses to the treatment. In addition, although clinical and laboratory differences are known, SARS Co-2 results in two different clinical pictures in the host immune system by causing COVID-19 and MIS-C. Therefore, further studies are needed to examine the immune system responses in more detail.

## Conclusion

When comparing MIS-C with pediatric COVID-19, distinctions in clinical presentation, laboratory findings, organ involvement, and treatments are evident. Our research demonstrates that these differences significantly affect the host's immune system. Notably, alterations in the lymphocyte subgroup within MIS-C are postulated to be indicative of the disease's clinical progression. Nonetheless, a more comprehensive exploration of this topic is warranted.

There are several limitations to our study. Firstly, the study encompassed only hospitalized patients, many of whom had concurrent medical conditions. Secondly, evaluations were restricted to the acute phase of the illness, though subsequent research intends to assess post-recovery changes. Lastly, the study did not undertake an exhaustive immune profiling, which would encompass cytokine analysis, activation markers, T cell repertoires, and transcriptomics, as a component of the immunological examination.

### Disclosures

**Ethics Committee Approval:** Ethical approval for this study was received from the Ondokuz Mayıs University Faculty of Medicine Clinical Research Ethics Committee (26.03.2021/26).

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**Conflict of Interest:** None declared.

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