Can Platelet Mass Index Be Used as a Prognostic Marker in Children Diagnosed with Multisystem Inflammatory Syndrome Associated with Coronavirus?

Koronavirus ile İlişkili Multisistem İnflamatuar Sendrom Tanılı Çocuklarda Trombosit Kitle İndeksi Prognostik Bir Belirteç Olarak Kullanılabilir mi?

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ABSTRACT

Objective: We've aimed at evaluating whether the platelet mass index (PMI) can be a prognostic marker for children diagnosed with MIS-C.

Material and Methods: 31 children diagnosed with MIS-C and treated at our university hospital between March 2020 and November 2021 were included. Demographic data, clinical findings and laboratory values at the time of hospitalization, admission to the intensive care unit and duration of hospitalization were evaluated retrospectively. PMI of each patient at the time of hospitalization was calculated and recorded.

Results: There was a statistically significant negative correlation between PMI and ferritin (r= -0.635, moderate, p<0.001), CRP (r= -0.377, weak, p= 0.036), and procalcitonin (r= -0.481, weak, p=0.006) levels. There was a statistically significant positive relationship between PMI and leukocyte count (r=0.367, weak, p=0.042) and lymphocyte count (r=0.384, weak, p=0.033). Median PMI values of the patients requiring intensive care (1701.35 fl/nl) were lower, compared to the median PMI values of the patients not requiring intensive care (2523.94 fl/nl), however, statistical results could not be reached due to the low (4 of 31) number of patients requiring intensive care. Median PMI values of the patients whose ferritin level was >400 ng/ml (1415.2; 533.4 – 3600.5) were statistically lower compared to the median PMI values of the patients whose ferritin level was ≤400 ng/ml (2705.7; 1395.2 – 9167.6).

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study Approval was obtained from the Turkish Ministry of Health General Directorate of Health Services COVID-19 Scientific Research Evaluation Board (Decision dated 17.11.2021 and numbered 2021-01-17T17_09_20).

Contribution of the Authors / Yazarların katkısı*: *EKER İ: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***BÜKÜLMEZ A:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***PEKTAŞ A:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***DÜZENLİ KAR Y:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study. ***EROĞLU N:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***ÇELEĞEN M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***ŞENOL Y:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study. ***ÇITAK A:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***GÜL B:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***SOYALAN B:*** Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***DURMUŞ D:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***KARATAŞ M:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study.

How to cite / *Atıf yazım şekli* : Eker İ, Bükülmez A, Pektaş A, Düzenli Kar Y, Eroğlu N, Çeleğen M, Şenol Y, Çıtak A, Gül B, Soyalan B, Durmuş D and Karataş M. Can Platelet Mass Index Be Used as a Prognostic Marker in Children Diagnosed with Multisystem Inflammatory Syndrome Associated with Coronavirus?. Turkish J Pediatr Dis 2023;17:257-262.

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Received / Geliş tarihi : 26.09.2022
Accepted / Kabul tarihi : 17.01.2023
Online published : 01.03.2023
Elektronik yayın tarihi
DOI: 10.12956/tchd.1180080

Conclusion: The findings in our study demonstrate that low PMI levels identified in children with MIS-C at the time of diagnosis may be with more severe clinical courses

Key Words: Child, Coronavirus Disease, Mass Index, Multisystem Inflammatory Syndrome, Platelet, Prognosis

ÖZ

Amaç: Trombosit kitle indeksinin (TKİ) MIS-C tanısı alan çocuklarda prognostik bir belirteç olup olmadığının değerlendirilmesi.

Gereç ve Yöntemler: Mart 2020 ile Kasım 2021 tarihleri arasında üniversite hastanemizde MIS-C tanısı konan ve tedavi gören 31 çocuk çalışmaya dahil edildi. Hastaneye yatış anındaki, yoğun bakıma yatış anındaki ve hastanedeki yatış süresince demografik veriler, klinik bulgular ve laboratuvar değerleri retrospektif olarak değerlendirildi. Her hastanın yatış anındaki TKİ değerleri hesaplandı ve kaydedildi.

Bulgular: TKİ ile ferritin (r= -0.635, orta, p<0.001), CRP (r= -0.377, zayıf, p= 0.036) ve prokalsitonin (r= -0.481, zayıf, p= 0.006) düzeyleri arasında istatistiksel olarak anlamlı negatif korelasyon bulundu. TKİ ile lökosit sayısı (r= 0.367, zayıf, p= 0.042) ve lenfosit sayısı (r= 0.384, zayıf, p= 0.033) arasında istatistiksel olarak anlamlı pozitif ilişki bulundu. Yoğun bakım gerektiren hastaların ortanca TKİ değerlerinin (1701.35 fl/nl), yoğun bakım gerektirmeyen hastaların ortanca TKİ değerlerinden (2523.94 fl/nl) istatistiksel olarak daha düşük olduğu saptandı (p= 0.005). Ferritin düzeyi >400 ng/ml olan hastaların ortanca TKİ değerlerinin (1415.2; 533.4 – 3600.5), ferritin düzeyi ≤400 ng/ml olan hastaların ortalama TKİ değerlerinden (2705.7; 1395.2 – 9167.6) istatistiksel olarak daha düşük olduğu saptandı (p= 0.005).

Sonuç: Çalışmamızdaki bulgular, MIS-C'li çocuklarda tanı anında tespit edilen düşük TKİ düzeylerinin, daha şiddetli klinik seyire yol açabileceğini ortaya koymaktadır.

Anahtar Sözcükler: Çocuk, Koronavirüs Hastalığı, Kitle İndeksi, Multisistem İnflamatuar Sendrom, Trombosit, Prognoz

INTRODUCTION

Upon understanding that the outbreak of the pneumonia epidemic in China in December 2019 was caused by a novel coronavirus type known as severe acute respiratory syndrome coronavirus (SARS-CoV-2), this disease was named "Coronavirus Disease 2019" (COVID-19). The epidemic was rapidly spread worldwide in a short time causing a pandemic (1). In April 2020, a severe disease presenting with findings of multiple organ involvement, rash, high fever, and high acute phase reactants, particularly in the gastrointestinal and cardiovascular systems was identified in children with previous COVID-19 infection. This presentation was named multisystem inflammatory syndrome associated with COVID-19 (MIS-C) by US Center for Disease Control and Prevention (2). While the etiology of MIS-C is similar to cytokine storm syndrome, macrophage activation syndrome, and Kawasaki disease, it is believed to be caused by an abnormal immune response to the virus. Covid-19 (SARS-CoV-2) Reverse Transcriptase PCR tests of most children diagnosed with MIS-C are negative and have positive serology. This suggests that MIS-C may be developed due to postviral immunologic responses, especially in cases with previous asymptomatic SARS-CoV-2 infection (3, 4).

There is a wide spectrum of the clinical picture in MIS-C due to its effect on multiple systems. Findings manifest weeks after the SARS-CoV-2 infection. Most cases are healthy and have no accompanying disease. It is generally prevalent in obese children. While fever is the most frequently identified finding, it is persistent and prolonged. It may be accompanied by gastrointestinal findings accompanied by vomiting, severe stomach aches and/or diarrhea, cardiac dysfunction, dehydration, mucocutaneous symptoms mimicking Kawasaki disease including conjunctivitis and rash, headache, neurological findings such as irritability and encephalopathy, and acute respiratory distress syndrome (ARDS). Some cases require intensive care due to hypotension and cardiac dysfunction requiring inotrope support. Moreover, there are reported cases with severe clinical conditions requiring extracorporeal membrane oxygenation (4).

Further tests must be done to confirm the MIS-C diagnosis in cases with the clinically suspected multisystem inflammatory syndrome in the presence of persistent high fever, history of encountering SARS-CoV, at least two of the following findings. These findings include rash (maculopapular), complaints of gastrointestinal systems (diarrhea, vomiting, stomach ache), changes in the oral mucosa (chapped and/or red lips, strawberry tongue or oropharyngeal mucosa erythema) bilateral nonexudative conjunctivitis, lymphadenopathy, meningism, papilledema, encephalopathy, changes in mental perception or focal neurological findings (2-4).

It is reported that approximately 60% of the children diagnosed with MIS-C need to be admitted to the intensive care unit, and unfortunately 2% result in mortality (5). It is determined that platelet counts and mean platelet volumes (MPV) of the patients can be used as a prognostic marker in COVID-19 infection just like in sepsis and severe diseases (6-9). It is demonstrated that the platelet mass index (PMI) calculated by using MPV, and platelet counts manifest the platelet functions much better compared to the platelet counts and MPV (10). Based on this, we aimed to evaluate whether PMI can be used or not as a prognostic marker in children diagnosed with MIS-C.

MATERIALS and METHODS

The statistical power analysis made for the study hypothesis identified that at least 19 patients with MIS-C needed to be included in the study to test the hypothesis with 80% power and 0.05 error. Required permits were obtained for the study from the Republic of Turkey Ministry of Health Directorate General of Health Services COVID-19 Scientific Research Evaluation

Committee (decision dated 17.11.2021 and numbered 2021-01-17T17_09_20), Afyonkarahisar University of Health Sciences (AFSÜ) Health Application and Research Center, and AFSÜ Clinical Researches Ethics Committee (decision dated 03.12.2021 and numbered 2021/13). 31 pediatric patients, diagnosed with MIS-C in accordance with the diagnostic criteria in the Republic of Turkey Ministry of Health COVID-19 Pediatric Patient Management and Treatment Guideline, and treated at AFSÜ Faculty of Medicine Department of Pediatric Health and Diseases between the dates of March 2020 and November 2021 were included in the study and hospital records of these patients were examined retrospectively (Table I) (11).

Demographic data of the patients, findings at the time of initial hospitalization, sedimentation rate, D-dimer, CRP, fibrinogen, LDH, ferritin, procalcitonin, albumin, troponin-T, pro-BNP levels, hemogram parameters, need for admission to the intensive care unit, intubation requirement, and duration of hospitalization were recorded. Platelet mass index (PMI) of each patient at the time of hospitalization was calculated and recorded using the formula [Platelet count] × [MPV / 1000] fl/nl (for example, platelet mass index of a patient with platelet count: 200 x 109/L and MPV: 9 fl is 1800 fl/nl) (10).

Statistical Package for the Social Science (SPSS 18.0 for Windows; SPSS Inc) was used for statistical analysis. The normal distribution test of continuous variables was performed by using the Shapiro-Wilk test. The Mann–Whitney U-test was used to test the difference between not normally distributed quantitative data, among the studied groups. Spearman correlation analysis was performed to detect correlational relations between variables where the assumption of the normal distribution is not provided. Correlation strength (positive or negative) was classified as 0.3–0.5 = weak, 0.5–0.69 = moderate, and 0.7–0.9 = strong correlation. The nonnormally distributed continuous data were reported as median (minimum-maximum). Categorical data are presented as numbers (n) and percentages (%). Statistical significance was defined as a two-tailed p value of<0.050.

Table I: Republic of Turkey Ministry of Health Guideline MIS-C Diagnostic Criteria

Multisystem Inflammatory Syndrome (Mis-C) Diagnostic Criteria
Being 0-21 of age
Fever measured >38.0 C persisting over 24 hours or presence of fever notified by the family
Evidence of inflammation in laboratory tests (presence of minimum 2 or more evidence)
High CRP
High sedimentation
High fibrinogen
High procalcitonin
High D-dimer
High ferritin
High LDH
High IL-6 level
Increased neutrophil count
Lymphopenia
Hypoalbuminemia
Severe disease setting requiring hospitalization
Multiple organ system involvements (presence of minimum 2 or more)
Cardiovascular (shock, high troponin, high BNP, abnormal ECHO findings, arrhythmia)
Respiratory (pneumonia, ARDS, pulmonary embolism)
Renal (Renal failure)
Neurologic (convulsion, stroke, aseptic meningitis)
Hematologic (coagulopathy, high D-dimer)
Gastrointestinal (high liver enzymes, diarrhea, ileus)
Dermatologic (erythroderma, mucositis, other rashes)
Absence of other alternative diagnoses (bacterial sepsis, infections associated with myocarditis such as enterovirus infection, staphylococcic, or streptococcal toxic shock syndromes)
Evidence of previous or current SARS-COV-2 infection (presence of at least one of the following)
SARS-COV-2 RT-PCR positive result
SARS-COV-2 serology positive result
SARS-COV-2 antigen-positive result
SARS-COV-2 positive case exposure within 4 weeks before onset of symptoms

CRP: *C-Reactive Protein,* ***LDH:*** *Lactate Dehydrogenase,* ***IL-6:*** *Interleukin-6,* ***BNP:*** *Brain natriuretic peptide,* ***ECHO:*** *Echocardiography,* ***ARDS:*** *Acute respiratory distress syndrome,* ***SARS-COV-2:*** *Severe acute respiratory syndrome coronavirus 2,* ***RT-PCR:*** *Real-time polymerase chain reaction.*

RESULTS

54.8% of the children (n=14) were male, and 45.2% (n=17) were female. The median age was 5.19 years, the youngest patient was three months of age, and the oldest patient was 18 years of age. While the median duration of hospitalization was 10 days, the shortest duration of hospitalization was 5 days, and the longest duration of hospitalization was 25 days. 12.9% of the children (n=4) required admission to the intensive care unit. While the median duration of the patients receiving treatment in the intensive care unit was 4.5 days, the shortest duration in the intensive care unit was 2 days, and the longest duration in the intensive care unit was 8 days. Laboratory values of the patients at the time of hospitalization are given in Table II.

Median platelet mass index of the patients at the time of hospitalization was 2172.6 (533.4-9167.6) fl/nl, median D-dimer level was 2.4 (0.0-32.9) ng/ml, median ferritin level was 424.1 (33.8-2466.0) ng/ml, median CRP level was 14.8 (0.1-273.5) mg/l, median procalcitonin level was 1.4 (0.1-56.7) ng/ml, median lymphocyte count was 1.5 (0.1-188.0) x 103/mm^3, and median sedimentation rate was 53.0 (11.0-142.0) mm/h.

It was identified that there was a statistically significant negative relationship between the platelet mass index and ferritin (r= -0.635, p<0.001, moderate), CRP (r= -0.377, p= 0.036, weak) and procalcitonin levels (r= -0.481, p= 0.006, weak) (Table III). In

Table II: Laboratory values of the patients at the time of hospitalization.

Laboratory Parameters	Values (n=31)
Platelet mass index (fl/nl)	2172.6 (533.4-9167.6)
D-dimer (ng/ml)	2.4 (0.0-32.9)
Ferritin (ng/ml)	424.1 (33.8-2466.0)
CRP (mg/l)	14.8 (0.1-273.5)
Sedimentation rate (mm/h)	53.0 (11.0-142.0)
Fibrinogen (mg/dL)	479.1 (149.8-739.0)
LDH (U/L)	319.0 (176.0-1101.0)
MPV (fl)	10.6 (8.2-12.8)
Platelet count (x10^3/mm^3)	204.0 (42.0-1118.0)
Erythrocyte count (x10^6/mm^3)	4.2 (3.2-5.3)
Leukocyte count (x10^3/mm^3)	9.7 (2.1-24.4)
Lymphocyte count (x10^3/mm^3)	1.5 (0.1-188.0)
Procalcitonin (ng/ml)	1.4 (0.1-56.7)
Albumin (g/dL)	3.4 (2.3-4.9)
Troponin-T (ng/ml)	0.0 (0.0-0.1)
proBNP (pg/ml)	1001.0 (11.9-35000.0)

Values are presented as median (minimum-maximum)

Table III: Relationship of platelet mass index with laboratory values.

	Platelet Mass Index (fl/nl)	
	r	p
Ferritin(ng/ml)	-0.635	<0.001
CRP (mg/l)	-0.377	0.036
Procalcitonin (ng/ml)	-0.481	0.006
Leukocyte count (x10^3/mm^3)	0.367	0.042
Lymphocyte count (x10^3/mm^3)	0.384	0.033

Table IV: Comparison of PMI and D-Dimer values based on admission to the intensive care unit

	Admission to Intensive Care	
	No (n:27)	Yes (n:4)
D-dimer level (ng/ml)	2.0 (0.0-8.9)	17.4 (4.9-32.9)
Platelet mass index (fl/nl)	2175.6 (750.0-9167.6)	1396.5 (533.4-3479.0)

Values are presented as median (minimum-maximum)

other words, it was identified that ferritin, CRP, and procalcitonin levels were increasing while PMI were decreasing and this was statistically significant (Figure 1).

It was identified that there was a statistically significant positive relationship between the platelet mass index and leukocyte count (r=0.367, p=0.042, weak) and lymphocyte count (r=0.384, p=0.033, weak) (Table III). In other words, it was identified that leukocyte count and lymphocyte count were decreasing while PMI of the patients were decreasing and this was statistically

Table V: Comparison of PMI values of the patients divided into two groups based on ferritin levels.

	Ferritin value(ng/ml) ≤400 (n:15)	Ferritin value(ng/ml) >400 (n: 16)	p
Platelet mass index values (fl/nl)	2705.7 (1395.29167.6)	1415.2 (533.4-3600.5)	0.002

Values are presented as median (minimum-maximum)

significant (Figure 2). No statistically significant relationship was identified between platelet mass index and D-dimer, fibrinogen, LDH, troponin-T, proBNP, albumin levels, sedimentation rate, and duration of hospitalization.

It was identified that the platelet mass index of the patients requiring admission to the intensive care unit was lower than the platelet mass index of the patients not requiring admission to the intensive care unit. And the D-dimer of the patients requiring admission to the intensive care unit was higher than the D-dimer of the patients not requiring admission to the intensive care unit. However, statistical results could not be reached due to the low number of patients requiring intensive care (Table IV).

When the patients were divided into two groups as ≤400 ng/ml (n:15) and >400 ng/ml (n:16) based on their ferritin levels, it was identified that the median platelet mass index (1415.2; 533.4 – 3600.5) of the group with ferritin level of >400 ng/ml was statistically lower than the median platelet mass index (2705.7; 1395.2 – 9167.6) of the group having ferritin level of ≤400 ng/ml (Table V). These results supported our findings that showed increasing ferritin levels of patients were accompanied by statistically significantly decreasing platelet mass index levels.

DISCUSSION

It is known that the MIS-C patients are asymptomatic during the active phase of COVID-19 or have mild respiratory symptoms, however, they develop multiorgan dysfunction within three to four weeks after the exposure to the virus, and this is caused by strongly activated T lymphocytes. A cytokine storm and cytotoxicity are developed as a result of such excessive activity of T lymphocytes. In addition, excessively activated T lymphocytes cause increased reactive oxygen radicals and oxidative stress along with monocyte and macrophages. Increased oxidative stress leads to changes and degradation in macromolecules such as DNA, proteins, and lipids. Furthermore, the presence of autoantibodies developed against the endothelial cells and leading to even more increased multisystem inflammation by causing endothelial dysfunction are among the important factors in the pathophysiology of MIS-C (12). Therefore, initial treatments involving intravenous immunoglobin (IVIG) and low-moderate dose steroid administration are recommended for most of the patients hospitalized due to MIS-C (13). Our findings

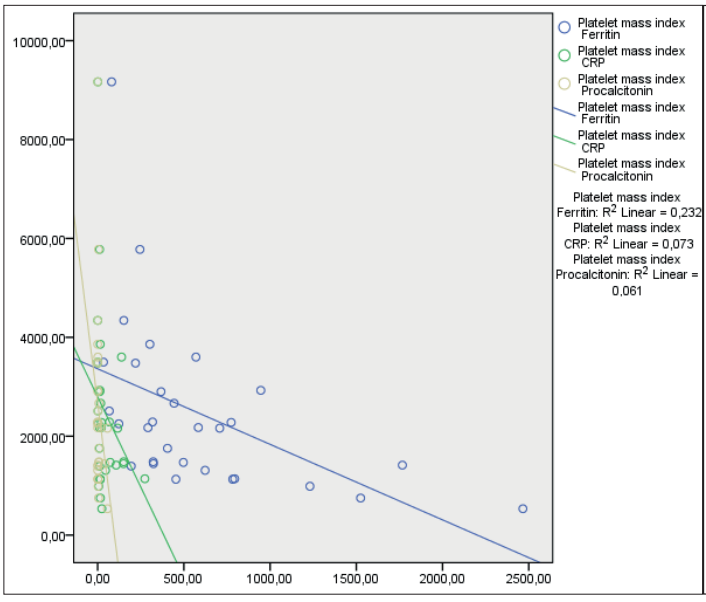

Figure 1: Platelet mass index and ferritin, CRP and procalcitonin level scatter plot.

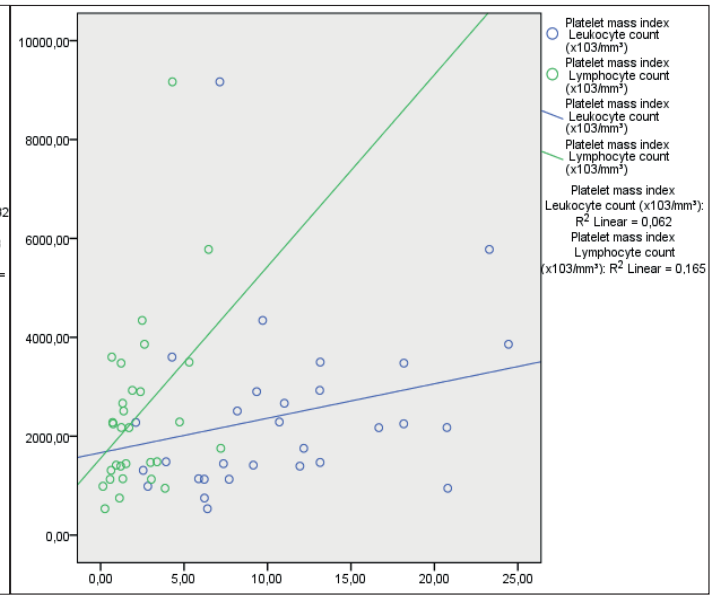

Figure 2: Platelet mass index and leukocyte count and lymphocyte count scatter plot.

in our study indicate that starting intravenous immunoglobulin and steroid treatment at an early stage in patients with low platelet mass index who are potential to be diagnosed with MIS-C may lead to a less severe course of the disease.

It is known that overproduction of pro-inflammatory cytokines and acute-phase reactants negatively affect the megakaryopoiesis leading to smaller and lesser platelet release from the bone marrow than normal (14). In the light of this information, we believe that hyperinflammation, the main factor of MIS-C pathophysiology, may cause smaller and lesser platelet release from the bone marrow of the patients, and decreased platelet volume and platelet count and platelet mass index which is calculated using these two parameters. In our study, we aimed to investigate the presence of such a condition in MIS-C and its relationship with the inflammation parameters. As a result, we have identified that the leukocyte counts, lymphocyte counts, and PMI of the patients statistically decrease as the ferritin, CRP, and procalcitonin levels increase. Our findings suggest that hyperinflammation in MIS-C and suppressed megakaryopoiesis through immune-mediated mechanisms, and thus the peripheral release of smaller and lesser platelets from the bone marrow may probably be the cause of low platelet mass index associated with MIS-C. Furthermore, our hypothesis is supported by the fact that the median platelet mass index (1415.2; 533.4 – 3600.5) of the group with ferritin level of >400 ng/ml is statistically lower than the median platelet mass index (2705.7; 1395.2 – 9167.6) of the group with ferritin level of ≤400 ng/ml.

Gu, et al. (15) reported that increased D-Dimer levels (fibrin degradation products indicating increased coagulation) and mild thrombocytopenia are observed in most patients requiring hospitalization due to COVID-19 infection, and the presence of high levels of D-Dimer along with severe thrombocytopenia is related to a more severe course of disease that leads to increase in the need for admission to the intensive care unit and mortality. Differently from the patients hospitalized due to COVID-19, most children diagnosed with MIS-C had negative COVID-19 PCR test while they had positive serological findings indicating that they had the infection. These findings indicate that hyperinflammation and secondary suppressing of megakaryopoiesis as a consequence are the prominent pathophysiologies in MIS-C in contrast with COVID-19 infection, in which the prominently common pathophysiologies are in coagulation. Furthermore, this demonstrates that lower platelet mass index values are accompanied by higher hyperinflammation levels and this may cause higher probability for the patients' with MIS-C to have worse outcomes.

Godfred, et al. (16) reported that the admission to the intensive care unit in children with MIS-C is 63.9%, and the mortality rate is 1.8%. Abrams, et al. (5) reported that the admission to the intensive care unit in children with MIS-C is 60%, and the mortality rate is 2%. In our study, the percentage of patients requiring admission to the intensive care unit is 12.9%, which is lower than what is reported in the literature. This can be explained by making an early diagnosis based on MIS-C suspicion and starting steroid and IVIG treatment in the early stage thus preventing the inflammatory storm stage and stabilizing the clinical course in the early stage. Likewise, we have seen that the duration of hospitalization had no relation with the platelet mass indexes of children diagnosed with MIS-C, and we have evaluated that this was based on two factors; i) starting the same treatment protocol in patients diagnosed with MIS-C in the clinic where this study was conducted, and ii) continuing their hospitalizations in the clinic until the end of this protocol schedule.

CONCLUSION

The findings in our study are valuable in demonstrating that, children with MIS-C who have lower PMI levels at the time of diagnosis have higher ferritin, CRP and procalcitonin levels. We can suggest that children with MIS-C who have lower PMI levels at the time of diagnosis have higher inflammatory status. This may lead to a more severe clinical course. Only 4 of 31 children in our cohort required admission to the intensive care unit. Because of this, it is impossible to evaluate statistically, but we identified that the median platelet mass index (1396.5 fl/nl) of the patients requiring admission to the intensive care unit was lower than the platelet mass index (2175.6 fl/nl) of the patients not requiring admission to the intensive care unit. These findings may support our suggestion. Thus, we believe that it will be useful if the physicians, who will be observing the children diagnosed with MIS-C, plan the treatment by taking into account the platelet mass index of the patients as well. Starting intravenous immunoglobulin and steroid treatment at an early stage in patients with low platelet mass index who are potential to be diagnosed with MIS-C may lead to a less severe course of the disease and may reduce the need for admission to the intensive care unit. Investigating the platelet mass index cut-off values in a broader population of cases that can anticipate the intensive care needs of the patients will greatly contribute to the literature on this subject.

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