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Original Article

The role of malnutrition on outcomes of multisystem inflammatory syndrome in children (MIS-C) due to COVID-19

Tutku Soyer[1], Kübra Aykaç[2], Gözde Özer[3], Yasemin Özsürekçi[2], H. Nursun Özcan[3], Kaya Yorgancı[4], Osman Abbasoğlu[4]

[1]Department of Pediatric Surgery, Faculty of Medicine, Hacettepe University, Ankara; [2]Department of Pediatric Infectious Diseases, Faculty of Medicine, Hacettepe University, Ankara; [3]Department of Pediatric Radiology, Faculty of Medicine, Hacettepe University, Ankara; [4]Department of General Surgery, Faculty of Medicine, Hacettepe University, Ankara, Türkiye.

ABSTRACT

Background. Malnutrition increases the complications and mortality in critically-ill children. We performed a retrospective analysis to define the impact of malnutrition on the outcomes of multisystem inflammatory syndrome in children (MIS-C) due to COVID-19.

Methods. Patients with MIS-C were evaluated for demographic features, anthropometric parameters, clinical findings and outcomes. Patients with z scores of body mass index (> 5 years) and weight-for-age (< 5 years) < -2 were considered malnourished. Sarcopenia was defined by total psoas muscle area (tPMA), calculated on abdominal computed tomography (CT) at the level of L3 and L4 vertebrae. The z scores <- 2 for tPMA were considered sarcopenia. The results of patients with and without malnutrition were compared.

Results. Twenty-seven patients were included. Forty-four percent (n=12) of patients had malnutrition. Malnutrition was classified as mild to moderate (1/3), severe (1/3) and overweight (1/3). Eighty-two % of cases had acute malnutrition. Among MIS-C symptom criteria, rash was significantly higher in children with malnutrition ($p<0.05$). Laboratory investigations showed higher ferritin levels in patients with malnutrition ($p<0.05$). The median tPMA and sarcopenia were significantly higher in patients with malnutrition when compared to patients without malnutrition (42% vs 7%, $p<0.05$). The oral feeding time, complication rates, and length of hospital stay were similar in both groups ($p>0.05$).

Conclusion. Children with MIS-C already had mild to severe malnutrition at admission. Rash and higher ferritin levels were more common in patients with malnutrition. In addition to anthropometric parameters, sarcopenia calculated using tPMA can be used to predict malnutrition in critically-ill children.

Key words: malnutrition, COVID-19, multisystem inflammatory syndrome, sarcopenia.

✉ Tutku Soyer
soyer.tutku@gmail.com

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The coronavirus disease 2019 (COVID-19) pandemic posed a great risk for healthcare systems and caused major morbidity and mortality. It has been reported that patients with severe COVID-19 had increased risk of malnutrition.[1] The prevalence of malnutrition is as high as 42% in COVID-19 infected patients and increases up to 66% in patients transferred from the intensive care unit.[2] Furthermore, malnutrition has detrimental effects on the prognosis of COVID-19 infection.[3] Malnourished

patients had worse outcomes and significantly higher in hospital-mortality compared to well-nourished adult COVID-19 patients.[3,4] As a result, several guidelines recommended early nutritional screening and adopted nutritional treatment for COVID-19 patients.[1,2]

Multisystem inflammatory syndrome in children (MIS-C) is a rare condition that often occurs 2 to 6 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[5] The definition of MIS-C includes evidence of severe illness, requiring hospitalization with at least two systems involvement. Acute COVID-19 has been shown to negatively affect the nutritional status of children. Longitudinal studies revealed that COVID-19 infections may cause various types of malnutrition in children.[6] Although the negative effect of COVID-19 infection on nutritional status has been well defined in adults, the impact of malnutrition on the clinical course and outcomes of MIS-C is not clear in the pediatric population.

In addition to anthropometric measures and serum protein levels, sarcopenia is also considered a component of malnutrition. It is characterized by reduced skeletal muscle mass and function.[7] Several methods have been used to defined to evaluate pediatric sarcopenia including dual energy X-ray absorptiometry and total psoas mass area (tPMA) measured on abdominal computed tomography (CT) scan.[8] The concept of sarcopenia is usually not taken into consideration in children. However, it facilitates the identification of children at risk for frailty and may help in the implementation of targeted treatments.[8] The role of malnutrition and sarcopenia has not been previously evaluated in children with MIS-C. Therefore, a retrospective study was performed to evaluate the nutritional status of children and its effect on clinical features and outcome of MIS-C.

Methods

Patients diagnosed with MIS-C between March 2019 – September 2022 were included in the study. The demographic features, anthropometric measurements, serum albumin levels, clinical findings of MIS-C, treatment options and outcomes (time to oral feeding, length of hospital stay and mortality) were retrospectively obtained from the hospital records. Sarcopenia was evaluated by tPMA on abdominal CT scans. Patients with and without malnutrition were compared for the abovementioned parameters. The study was approved by the Local Ethical Committee (GO/2022-20-22).

MIS-C definition

According to the definition of Center for Disease Control and Prevention (CDC), patients with the below criteria were diagnosed with MIS-C.[9]

- an individual aged <21 years presenting with fever (≥38.0 °C for ≥24 hours, or report of subjective fever lasting ≥24 hours),
- laboratory evidence of inflammation [including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin]
- evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological),
- No alternative plausible diagnoses; and
- Positive for current or recent SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

Inclusion criteria

1. Patients who meet the MIS-C criteria mentioned above

2. Patients with no history of chronic illness and/or cancer
3. Patients with an abdominal CT scan on admission

Exclusion criteria

1. Patients who do not meet MIS-C criteria
2. Patients with previous chronic illnesses and/or cancer
3. Patients with no abdominal CT scan.

Anthropometric measurements

The body weight, height, and body mass index (BMI) measured on admission were noted from medical records. The z scores for BMI, weight-for-age (WFA), height-for-age (HFA) and height-for-weight (HFW) were calculated according to the validated percentiles for Turkish children.[10] The definition of malnutrition was based on z scores of BMI in children > 5 years and on height-for-weight in children < 5 years. According to WHO definitions, patients were classified as normal nourished (-2 > z score < 2), minimum – mild malnutrition (z score = - 2 / -3), severe malnutrition (z score > -3) and overweight (z scores ≥ 3).[11] All children with malnutrition were also classified as having acute (BMI and/or HFW) or chronic (HFA) malnutrition (z scores < -2).

Evaluation of sarcopenia

In this study, CT scans were used to evaluate sarcopenia in children. CT scans were obtained to have a differential diagnosis of acute abdomen and GI involvement during the clinical course of COVID-19 and none of the patients underwent CT scan to assess their nutritional status. Abdominal CT scans were performed using a GE LightSpeed 16-slice CT scanner (GE Healthcare, Milwaukee, WI) and examinations were evaluated by pediatric radiologists after retrieval from the hospitals' picture archiving and communication system (PACS) (GE Medical Systems, Milwaukee, WI). The left and right psoas muscle areas were measured at L3-4 and L4-5 levels on transverse view.[12] The area was measured in mm^2 with the region of interest (ROI) measurement tool from each side (Fig. 1). The sum of both sides was obtained to have total psoas muscle areas (tPMA). The z scores of tPMA were calculated by using Pediatric Total Psoas Muscle Area (tPMA) z-score calculator' (https://ahrc-apps.shinyapps.io/sarcopenia).[13] Sarcopenia was defined as tPMA z scores < -2.[12]

Statistics

For statistical analysis, the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, USA) was used. The descriptive values were calculated as means ± standard deviations and medians (with interquartile ranges: Q1-Q3) within a 95% confidence interval. Patients with and without malnutrition were compared with chi-square test and non-parametric tests according to normality distribution, which was Mann-Whitney U test for our two groups. The p values <0.05 were considered statistically significant.

Results

Twenty-seven patients met the inclusion criteria. The mean age of the patients was 9.4 ± 4.61 years (2-16 y) and male - female ratio was 15:12. According to the above definition, 44% (n=12) of patients had malnutrition. Table I shows the demographic features, median

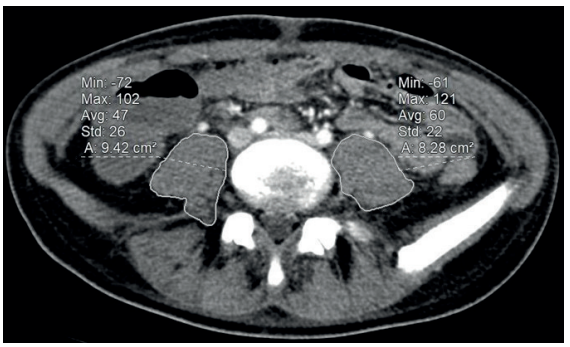

Fig. 1. Transverse contrast enhanced abdominal CT image shows bilateral psoas muscle area measurement at L4-5 level.

Table I. Demographic features, anthropometric measurements and serum protein levels in patients with and without malnutrition.

	Patients with malnutrition (n:12)	Patients without malnutrition (n:15)	P values
Age (year), median (Q1-Q3)	5.5 (4-10.25)	10 (6-13)	0.96
Gender (male: female)	6:6	9:6	0.70
Anthropometric measurements, median (Q1-Q3)			
Weight (kg)	22.5 (17,2-34.2)	45 (21-56)	0.02*
Height (cm)	122.5 (102.5-155.2)	150 (110-163)	0.27
BMI (kg/m^2)	16.5 (13.7-22.7)	19.6 (17.9-23.1)	0.14
BMI z score	-1.19 (-1.95-1.63)	0.85 (-0.13-1.72)	0.17
WFA z scores	0.25 (-1.22-0.68)	0.79 (0.22-1.33)	0.14
HFA z scores	0.99 (0.22-2.71)	0.93 (-0.47-1.21)	0.54
Acute chronic malnutrition	10:2 (83.3% : 16.7%)		
Classification of malnutrition, n (%)			
Mild- moderate	4 (33.3%)		
Severe	4 (33.3%)		
Overweight	4 (33.3%)		
Serum albumin level (mg/dl), median (Q1-Q3)	3.15 (2.59-3.39)	3.22 (2.83-3.85)	0.36

*p<0.05. BMI: body mass index, HFA: height-for-age, WFA: weight-for-age.

anthropometric measurements, and serum albumin levels in patients with and without malnutrition. Patients with and without malnutrition had similar median age and gender distributions. Patients with malnutrition were classified as mild to moderate (1/3), severe (1/3) and overweight (1/3). Eighty-two % of cases had acute malnutrition. Two patients had chronic malnutrition. When anthropometric measurements were compared, patients without malnutrition had a significantly higher median weight compared to patients with malnutrition ($p< 0.05$).

The MIS-C parameters and serum levels of inflammatory markers are listed in Table II. Among the MIS-C criteria, rash was significantly higher in patients with malnutrition ($p<0.05$). Median levels of ferritin were significantly higher in patients with malnutrition when compared to patients without malnutrition (1106.2 μg/l vs 276.1 μg/l, respectively $p < 0.05$). The comparison of inflammatory markers in both groups is summarized in Fig. 2. Ferritin levels were significantly higher in patients with malnutrition compared to patients without malnutrition ($p>0.05$). The oral feeding time, complication rates and length of hospital stay were similar in both groups. There was no mortality in both groups.

Table III shows the median levels of tPMA measurements obtained from L3-4 and L4-5 levels. The median levels of tPMA were significantly lower in patients with malnutrition (Fig. 3, $p<0.05$). Forty-two % of patients with malnutrition and 7% of patients without malnutrition had sarcopenia (z scores of tPMA <-2). However, median z scores of tPMA were not significantly different between groups (Fig. 3, $p>0.05$). When patients with and without sarcopenia were compared, there was no difference in outcomes of MIS-C in terms of time to oral feedings, length of hospitalization and mortality ($p>0.05$).

Discussion

In this study, we found that nearly half of the children with MIS-C had mild to severe malnutrition on admission and sarcopenia was observed in a significant number of these

Table II. Comparison of MIS-C findings, outcomes and median levels of serum inflammatory markers.

Parameters	Patients with malnutrition (n:12)	Patients without malnutrition (n:15)	p values
MIS-C criteria, n (%)			
- Fever	12 (100%)	15 (100%)	-
- GI symptoms	12 (100%)	15 (100%)	-
- Rash	12 (100%)	7 (47%)	0.03*
- Respiratory symptoms	1 (8%)	5 (33%)	0.18
- Neurologic findings	0	3 (20%)	0.23
- Cardiac involvement	4 (33%)	6 (40%)	0.51
- Renal involvement	1 (8.3%)	2 (13.3%)	0.58
Inflammatory markers, median (Q1-Q3)			
CRP (mg/dL)	18.2 (10.9-23.6)	13.6 (12.5-24.3)	0.77
Procalcitonin (ng/mL)	18.4 (2.5-28.9)	4.48 (0.69-13.8)	0.07
Lymphocyte count (x10^3/μL)	850 (600-1475)	700 (300-1300)	0.19
Thrombocyte count (x10^3/μL)	142 (118-183)	182 (106-290)	0.51
D-dimer (mg/L)	3.91 (1.94-7.17)	4 (2.03-7.05)	0.93
Ferritin (μg/l)	453.1 (292.8-1447.1)	215.3 (170.7-864)	0.04*
INR	1.17 (1.03-1.33)	1.25 (1.11-1.43)	0.19
Outcomes, median (Q1-Q3)			
Time to oral feeding (days)	2 (2-2.75)	2 (1-3)	0.52
Length of hospital stay (days)	7 (6-8)	9.4 (6-11)	0.42
Mortality (n)	0	0	-

*p<0.05. CRP: C-reactive protein, GI: gastrointestinal, INR: international normalized ratio.

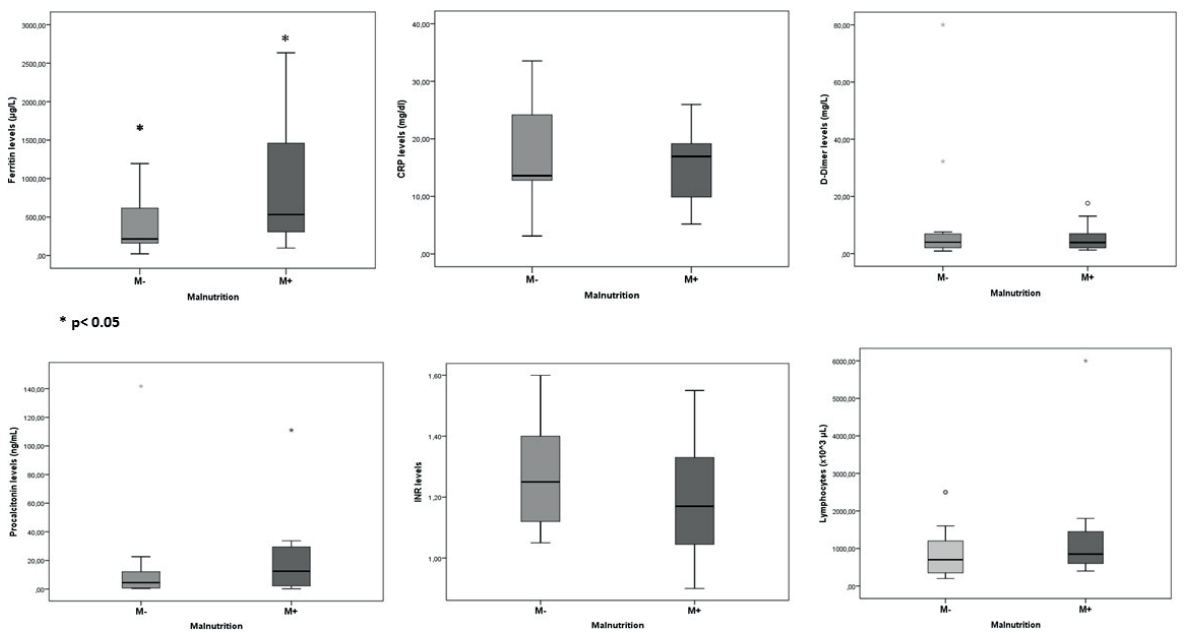

Fig. 2. Comparison of inflammatory markers in patients with and without malnutrition.

Table III. Sarcopenia, the right, left and total PMA in patients with and without malnutrition.

	Patients with malnutrition (n:12)	Patients without malnutrition (n:15)	P values
Psoas muscle area (mm^3), median (Q1-Q3)			
Right L3-4	3.66 (3.02-5.16)	6.08 (4.08-7.65)	0.01*
Left L3-4	3.73 (2.92-5.33)	6.29 (4.27-7.95)	0.03*
tPMA L3-4	7.40 (6.11-10.49)	12.32 (8.1-15.6)	0.02*
Right L4-5	4.46 (3.76-5.94)	7.44 (5.11-10.1)	0.02*
Left L4-5	4.47 (3.66-6.37)	7.75 (5.14-10.1)	0.03*
tPMA L4-5	8.93 (7.17-12.2)	15.1 (10.2-19.1)	0.02*
Z scores for sarcopenia, median (Q1-Q3)			
Z score for sarcopenia L3-4	- 1.24 (-1.89- -0.32)	-0.62 (-1.2 – 0.16)	0.22
Z score for sarcopenia L4-5	-1.21 (-1.83- -0.33)	-0.77 (-1.67- 0.7)	0.35
Presence of sarcopenia, n (%)	5 (42%)	1 (7%)	0.04*

*p<0.05. tPMA: total psoas muscle area.

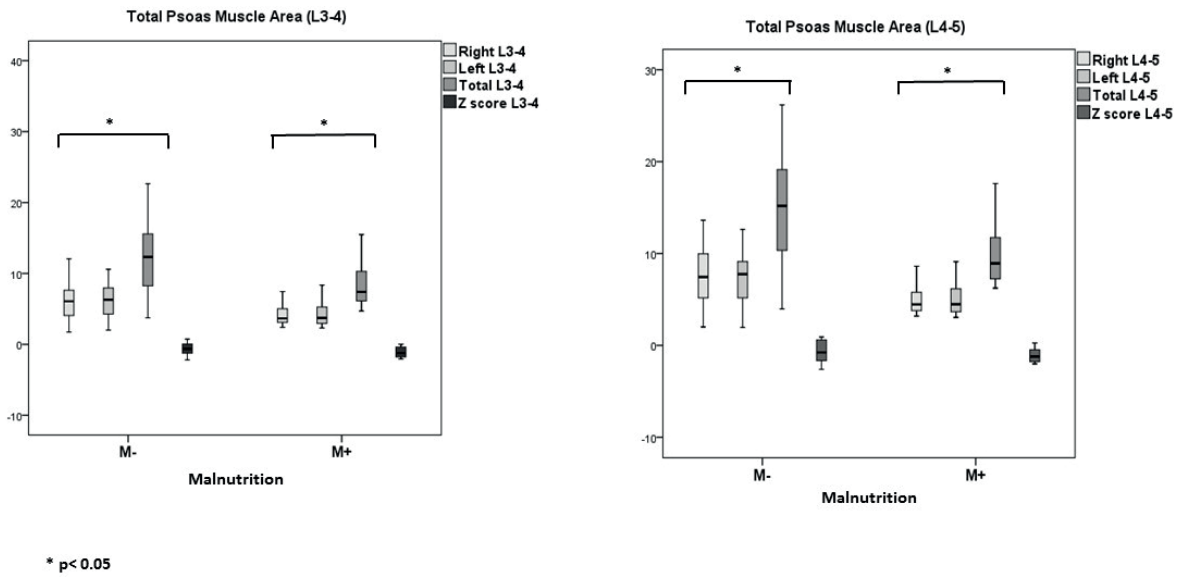

Fig. 3. The measurement of right, left and total psoas muscle area and z scores at the level of L3-4 and L4-5 vertebrae. Comparison of patients with and without malnutrition.

patients. During the COVID-19 pandemic, some of the children with SARS-CoV-2 infection developed MIS-C and faced severe morbidity, whereas most of the others neither had severe disease nor developed multisystem failure. To date, the underlying mechanisms and risk factors for developing MIS-C are not known. Malnutrition remains one of the risk factors for worse outcomes in critically-ill children.[13] Moreover, critically-ill patients with COVID-19 are at high risk of malnutrition due to the illness itself and significant metabolic alterations.[14] Although several guidelines have underlined the importance of nutritional management for COVID-19 patients in the adult population, the nutritional status and its impact on outcomes of MIS-C have not been elucidated previously. In this study, we found that 44% of children with MIS-C had mild to severe malnutrition on admission. Eighty-three percent of patients had acute malnutrition whereas only two children had chronic malnutrition. This suggests

that acute malnutrition might be a result of COVID-19, since the patients were healthy children and had no chronic diseases. The outcome of overweight patients was also similar to that of the undernourished patients. Thus, the findings of our study are not sufficient to claim that malnutrition is a risk factor for developing MIS-C, and patients with malnutrition had worse outcomes. However, screening of nutrition and adapting a nutritional supportive care should be provided for all MIS-C patients to overcome the catabolic process.

Children with MIS-C present with a wide range of clinical features and more than two systems should be involved in the diagnosis. When we compared the clinical findings with the nutritional status of children, we found that rash was seen in almost all patients with malnutrition and was significantly higher than in patients without malnutrition. Rekhtman et al.[15] reported that children with rash had less severe disease, fewer intensive care unit admissions, less shock and better outcomes when compared to children without rash. In that cohort, children with rash had less cardiac involvement. According to these contradictory results, it is not possible to conclude that the presence of rash is associated with better outcomes. Although the relation between higher incidence of rash in patients with malnutrition and outcome is not clear, the high number and heavy distribution all over the body and late improvement of rashes during the treatment period were some of our important observations in the present series. Furthermore, malnutrition may impair the immune response trigger the underlying immune mechanism of mucocutaneus findings, which may support our clinical findings.

MIS-C is characterized by a hyperinflammatory response with high levels of several inflammatory markers. Compared to COVID-19 patients, MIS-C patients had lower LDH and platelet levels and higher ESR.[16] Moreover, severe MIS-C patients had higher serum levels of white blood cell counts, absolute neutrophil count, CRP, D-dimer and ferritin levels.[16] In the present study, we observed that ferritin levels were significantly higher in patients with malnutrition when compared to patients without malnutrition. Since other inflammatory markers showed no difference with and without malnutrition in MIS-C, higher ferritin levels can be considered a sign of inflammation and malnutrition instead of a higher risk of severe MIS-C.

In addition to anthropometric features and serum protein profiles, sarcopenia is an important feature of malnutrition. The term 'sarcopenia' defines both reduced skeletal muscle mass and function.[8] However, the concept of sarcopenia is underestimated and is associated with poor outcomes in the pediatric population. Although we could not show any significant correlation between sarcopenia and the outcome of MIS-C, we suggest that sarcopenia diagnosed on tPMA can be used to predict malnutrition in critically-ill children, if an abdominal CT scan is obtained for any other reason.

Our study has some limitations. Firstly, a small number of patients were included in the analysis. A larger cohort of patients is needed to show the role of malnutrition on clinical features and outcomes of MIS-C. Therefore, it may not be possible to conclude that malnutrition is associated with a worse outcome. Secondly, to demonstrate an association between malnutrition and clinical and laboratory findings of MIS-C, additional parameters including immune and hematologic functions may be required. Also, the physical activity of the children during pandemic should be taken into consideration while evaluating sarcopenia in MIS-C patients. Despite these limitations, to the best of our knowledge this is the first study investigating the role of malnutrition including sarcopenia in MIS-C patients.

In conclusion, children with MIS-C due to COVID-19 had mild to severe malnutrition on admission. Rash and higher ferritin levels are more common in patients with malnutrition. The tPMA measurement can be used to predict sarcopenia in critically-ill children.

Ethical approval

The study was approved by Local Ethical Committee of Hacettepe University (GO/2022-20-22).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: TS, KA, YÖ, KY, OA; data collection: KA, GA, YÖ, HNÖ; analysis and interpretation of the results: TS, GÖ, HNÖ, KY, OA; draft manuscript preparation: TS, KA, YÖ, HNÖ, KY, OA. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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