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Original Article

Evaluation of thymic dimensions in patients with multisystem inflammatory syndrome

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ABSTRACT

Background. Multisystem inflammatory syndrome (MIS-C) is the most important complication of COVID-19 in the pediatric population. Unfortunately, this problem is an unpredictable situation in patients with COVID-19. We aimed to evaluate the effects of MIS-C on thymus dimensions in pediatric patients.

Methods. We retrospectively analyzed the files of 368 pediatric patients aged 2-18 years, who were diagnosed with COVID-19. Computer Tomography (CT) images of 22 patients diagnosed with COVID-19 and 10 patients diagnosed with MIS-C were evaluated in detail by two board-certified radiologists. Eighteen age and sex-matched patients who applied to the emergency department of our hospital for any reason and had a CT scan for any reason were selected as the control group. The data of both groups were statistically compared.

Results. Considering the differences between the groups in terms of laboratory data, monocytes, hemoglobin, and platelet were significantly lower in the MIS-C group than the other groups. Procalcitonin, C- reactive protein, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and proBNP levels were statistically significantly higher in the MIS-C group compared to the other groups Regarding the differences in thymus dimensions, thymus AP diameter, transverse diameter, length, thickness, and volume were significantly higher in the MIS-C group than in the other groups There was a significant positive correlation between the transverse diameter of the thymus and CRP, procalcitonin, pro-brain natriuretic peptide (proBNP), and NLR levels.

Conclusions. Our study shows that thymus dimensions and acute phase reactants are higher in pediatric patients in the MIS-C group. Also, thymus transverse diameter, thymus thickness, and PLR values pose a risk for the development of MIS-C. More research is needed on the role of the thymus gland in the pathogenesis and diagnosis of MIS-C.

Key words: pediatric patient, COVID-19, multisystem inflammatory syndrome in children, thymus.

The thymus, a lymphoid organ, is responsible for the formation and development of T cells. The process of change of the thymus begins when the progenitor cells enter the thymus with blood vessels in the cortico-medullary region. T cell development begins with the binding of the antigen to the T cell receptor (TCR). It is also the primary determinant of the fate of thymocytes. Thymocytes can be monitored for the presence or absence of surface markers such as CD4 and CD8. The maturing cells leave the thymus and migrate to peripheral lymphoid organs such as lymph nodes, spleen, and submucosal lymphoid tissue.[1,2] The thymus is very sensitive to endogenous or exogenous factors (infections, malnutrition). Depending on these changing factors, peripheral immune responses are likely to be impaired. Unfortunately, current studies are insufficient to evaluate the reflections of diseases on the thymus and its role in disease pathophysiology, focusing rather on the peripheral immune system.[1,3] The thymus, the producer of T lymphocytes, is particularly

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susceptible to infections because of its important function. There is evidence in the literature showing that viral pathogenic microorganisms can change thymic structure and physiology.[4-7] The pathophysiology of multisystem inflammatory syndrome (MIS-C) is currently not clarified. Initially asymptomatic or with mild symptoms in children, the infection may cause stimulation of helper T cells and activation of macrophages. In some children, this infection causes excessive release of cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1β, 4, 6,12, 18, 23, interferon (IFN), and stimulation of macrophages. In addition, caspase 1, which causes stimulation of neutrophils and monocytes, is often co-produced with IL-1β in children with MIS-C. Increased levels of IL-18, which is converted from pro-IL-18 to IL-18 through its activation. IL-18 increases IFN levels and functional activities. Increased IL-18 and IFN levels and the cytokine storm can be seen in MIS-C.[8-10]

Currently, there is no sufficient number of articles in the literature showing the relationship between COVID-19 and MIS-C and thymus dimensions. Therefore, we aimed to evaluate the effects of COVID-19 and MIS-C on thymus dimensions in pediatric patients to develop new perspectives for the pathogenesis, treatment and prevention of MIS-C while the COVID-19 pandemic is still ongoing.

Material and Methods

Study group

This study is a retrospective single-center observational study. We retrospectively reviewed the files of 368 pediatric patients aged 2-18 years who were diagnosed with COVID-19, were positive for the COVID-19 PCR test and/or COVID-19 antibodies, and were examined at the time of admission. The files of patients admitted to the Pediatric Emergency Department between March 2020 and May 2021 were reviewed retrospectively. Pediatric patients with COVID-19, diagnosed with MIS-C according to the criteria of the World Health Organization (WHO) and Center for Disease Control and Prevention (CDC), with cardiac markers and chest computed tomography (CT) were included in the study.[11,12] Findings were obtained from hospital records. CT images of 22 patients diagnosed with COVID-19 and 10 patients diagnosed with MIS-C were evaluated in detail by two board-certified radiologists. Patients over 18 years of age, those without CT images, those with poor quality CT images, immunocompromised patients, those with liver failure, kidney failure, hematologic and/or oncologic disease, chronic obstructive pulmonary disease, and those whose COVID-19 PCR or COVID-19 antibodies were not investigated for the presence of COVID-19 were excluded.

Age and gender-matched patients who applied to the emergency department of our hospital due to trauma or non-opaque foreign body ingestion and who received a thoracic CT were selected as the control group. None of these patients had a lower respiratory tract infection COVID-19 and/or MIS-C clinic and diagnosis. Eighteen pediatric patients who met the criteria were selected as the control group.

The cases included in the study were grouped according to their ages as 2-6 years, 7-13 years, and 13-18 years.[13]

Computed tomography

Contrast-free CT images were obtained using a standard thorax CT protocol, 130 kVp regulating tube voltage, 100–350 mA tube current, a slice thickness is 3mm, 25 cm scanning field of view (FOV) and a 512×512 matrix with a high resolution thorax algorithm of a 64 detector array scanner (LightSpeed VCT, GE Medical Systems, Milwaukee, WI, USA).

Image evaluation and analysis

Thymus size and volume were evaluated in the axial plane on thorax CT images (using a 27-inch iMac computer, Apple Inc. Cupertino, 88 California, USA). Thymus volume was

calculated from the relevant region (ROI) mentioned in the literature in each case Fig. 1.[14] Quantitative measurements of the thymus (length and thickness of the right and left lobes of the thymus, width-length and anterior posterior diameters of the gland) were made by two radiologists from CT images. Diameter, length and thickness measurements of the thymus were made according to the definitions published in previous studies (Fig. 2).[15]

Laboratory data analysis white blood cell count (WBC), lymphocyte, monocyte, neutrophil, neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMO), hemoglobin (Hb), platelet (PLT), platelet-lymphocyte ratio (PLR), C-reactive protein (CRP), procalcitonin, and pro-brain natriuretic peptide (proBNP) values were analyzed retrospectively.

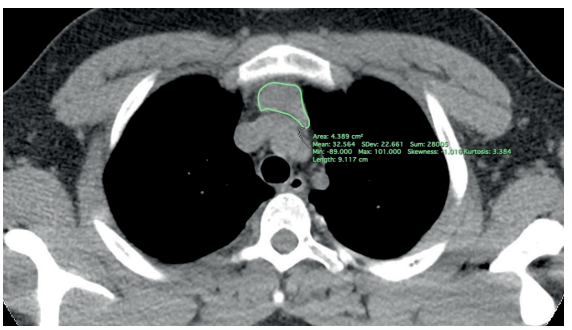

Fig. 1. The thymic volume was calculated in each case from the region of interest thorax axial CT images.

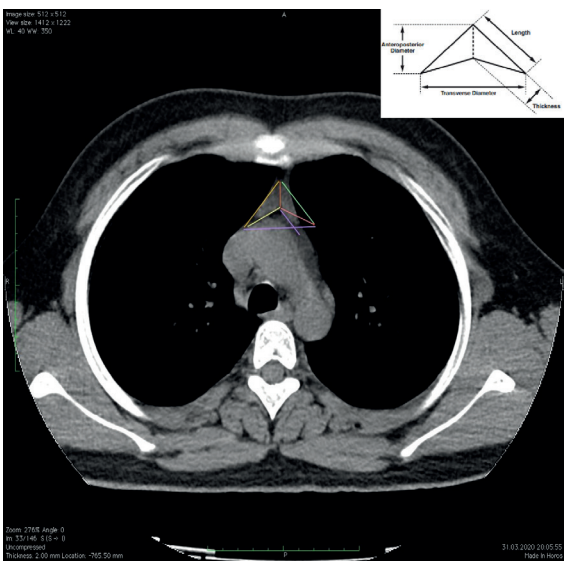

Fig. 2. Thymus thickness, anteroposterior diameter, transverse diameter and length measurement on thorax axial CT images.

The study was conducted in accordance with the principles stated in the Declaration of Helsinki. Ethical approval was obtained from the Ministry of Health and the local ethics committee of Kahramanmaras Sütcü İmam University before the study (Ethics committee date: 26.03.2021, Session: 2021/2022, Protocol no: 185, Decision no: 03)

Statistical analysis

Statistical data analysis was performed using SPSS 22 software. Descriptive statistics were presented as continuous variables (mean ± standard deviation) and categorical variables (%). Chi-square test and Fisher's exact test were used for the analysis of categorical variables. The Mann–Whitney U test was used to compare non-normally distributed continuous variables. Kolmogorov-Smirnov test was performed to check for normal distribution in continuous variables. A one-way ANOVA test was used to determine the difference of the mean value of a dependent variable between two independent groups. Correlation analysis was performed to determine the severity and direction of the relationship between two numerical variables. Pearson correlation coefficient was preferred for normally distributed data and Spearman rank correlation coefficient was preferred for non-normally distributed data. Receiver operating characteristic (ROC) curve analysis was performed to find the optimal cut-off, sensitivity, and specificity of the PLR and thymus dimensions in predicting MIS-C. For all tests, $p<0.05$ was considered statistically significant.

Results

Considering demographic and diagnostic data, the mean age of the patients was 10.85±4.52 years and there was no significant difference between the groups in terms of age or sex ($p=0.718$, $p=0.628$, respectively). COVID-19 PCR

(+) was detected in 19 (86.4%) of the patients in the COVID-19-infected non-MIS-C group and COVID-19 IgM was positive in 3 (13.6%). In the MIS-C group, PCR was positive in 3 patients (30%) and COVID-19 IgM was positive in 7 (70%). These diagnostic differences were statistically significantly different between the groups. Monocyte, Hb, and PLT were significantly lower in the MIS-C group than in the other groups. Procalcitonin, CRP, NLR, PLR, and proBNP levels were statistically significantly higher in the MIS-C group compared to the other groups (Table I). Considering the differences in thymus dimensions, thymus AP diameter, transverse diameter, length, thickness, and volume (Fig. 3) were significantly higher in the MIS-C group than in the other groups (Table II). When the relationship between laboratory findings and thymus dimensions was evaluated; There was a significant positive correlation between thymus transverse diameter and CRP, procalcitonin, proBNP and NLR. While there was a significant positive correlation between thymus length and CRP and NLR, there was a significant positive correlation between thymus thickness and CRP, proBNP and NLR. There was a significant positive correlation between thymus volume and CRP. However, there was no correlation between thymus AP diameter and laboratory findings (Table III). When the thymic dimensions were evaluated according to age groups, there was no statistically significant difference between the groups in terms of AP diameter, transverse diameter, length, thickness, or volume in the 2-6 age group. In the 7-13 age group, the AP diameter of the thymus was significantly higher in patients with COVID-19 and the transverse diameter and thickness of the

Table I. Comparison of laboratory data by groups.

	Control (n=18)	COVID-19 (n=22)	MIS-C (n=10)	P
WBC	8.97±4.74	8.85±3.83	10.27±5.81	0.702
Neutrophil	5.47±4.25	5.83±3.80	8.23±6.09	0.276
Lymphocyte	2.65±1.22	2.10±1.41	1.64±2.15	0.239
Monocyte	644.71±359.91	762.73±287.54	328.00±186.95	0.002
Hb	12.85±1.40	13.29±1.20	11.90±1.15	0.021
PLT	291.11±64.69	256.45±60.47	206.50±78.82	0.009
CRP	3.05±1.40	6.89±9.83	133.67±115.10	0.001
Procalcitonin	0.035±0.007	0.060±0.046	8.56±12.93	0.019
NLR	2.44±2.05	3.99±3.72	8.85±5.68	0.001
LMO	4.59±2.09	3.15±2.09	4.53±2.60	0.093
PLR	120.73±49.74	154.45±74.45	188.59±61.45	0.031
ProBNP	0.00±0.00	160.63±294.99	9976.80±8959.15	<0.001

Oneway ANOVA. Post Hoc Test (Scheffe)
CRP: C-reactive protein, Hb: hemoglobin, LMO: lymphocyte-monocyte ratio, MIS-C: multisystem inflammatory syndrome, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio. ProBNP: pro-brain natriuretic peptide

Table II. Evaluation of thymus sizes by groups.

Thymus sizes	Control (n=18)	COVID-19 (n=22)	MIS-C (n=10)	P
AP diameter	1.20±0.29	1.39±0.32	1.47±0.18	0.039
Transverse diameter	3.67±0.35	2.96±0.91	4.66±0.84	<0.001
Length	2.29±0.36	2.09±0.64	2.84±0.59	0.003
Thickness	0.94±0.12	0.92±0.13	1.12±0.09	<0.001
Volume	12.46±3.11	9.88±4.45	14.71±4.06	0.007

Oneway ANOVA. Post Hoc Test (Scheffe)
AP: anterior-posterior, MIS-C: multisystem inflammatory syndrome

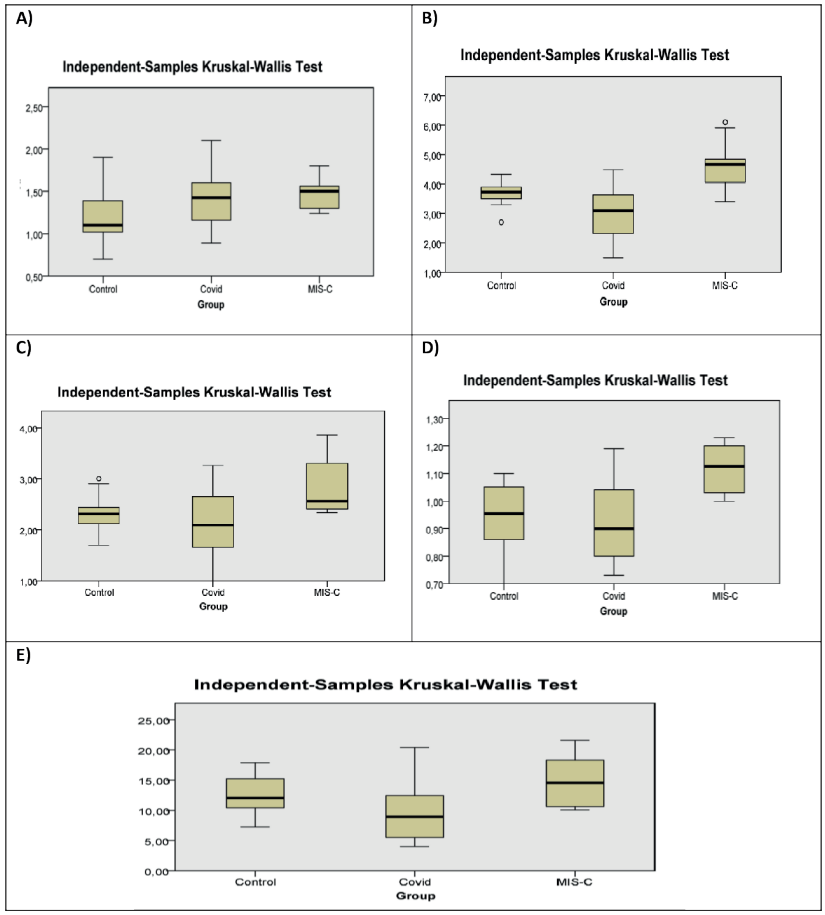

Fig. 3. A) Thymus AP diameter was significantly larger in the MIS-C group (p=0.033). B) Thymus transverse diameter was significantly higher in the MIS-C group (p<0.001). C) Thymus length was significantly higher in the MIS-C group (p=0.004). D) Thymus thickness was significantly higher in the MIS-C group (p=0.001). E) Thymus volume was significantly higher in the MIS-C group (p<0.001).

Table III. Evaluation of the relationship between the thymus dimensions of the patients and the laboratory data.

Thymus sizes		CRP	Procalcitonin	ProBNP	WBC	NLR	PLR	LMO
AP diameter	r	0.172	-0.027	0.221	0.098	0.221	0.246	-0.261
	p	0.308	0.884	0.182	0.564	0.127	0.141	0.070
Transverse diameter	r	0.596	0.379	0.416	0.166	0.367	0.094	0.174
	p	<0.001	0.036	0.009	0.326	0.009	0.582	0.232
Length	r	0.527	0.239	0.282	0.204	0.352	0.094	0.099
	p	0.001	0.195	0.086	0.225	0.013	0.579	0.499
Thickness	r	0.470	0.285	0.496	0.108	0.312	0.064	0.099
	p	0.003	0.120	0.002	0.525	0.029	0.706	0.499
Volume	r	0.362	0.203	0.226	0.040	0.123	-0.121	0.249
	p	0.030	0.282	0.178	0.818	0.404	0.481	0.087

Correlations. Pearson Correlation
CRP: C-reactive protein, Hb: hemoglobin, LMO: lymphocyte-monocyte ratio, MIS-C: multisystem inflammatory syndrome in children, NLR: neutrophil-lymphocyte ratio, PLR: platelet- lymphocyte ratio, ProBNP: pro-brain natriuretic peptide

thymus were statistically significantly higher in the MIS-C group compared to the other groups There was no significant difference between the groups in terms of thymus length or volume. In the 14-17 age group, there was no statistically significant difference in terms of AP diameter, thickness, or volume. The thymus transverse diameter and length were significantly higher in the MIS-C group (Table IV). A ROC curve analysis was performed to determine the best cut-off points for thymus dimensions and PLR levels to predict MIS-C. Accordingly, we found that if the AP diameter of the thymus tissue is ≥1.230 cm, it can predict MIS-C with 100% sensitivity and 47.5% specificity. We found that if the transverse diameter of the thymus tissue is ≥4,030 cm, it can predict MIS-C with 80% sensitivity and 92.5% specificity We found that if the length of the thymus tissue is ≥2.330 cm, it can predict MIS-C with 100% sensitivity and 62.5% specificity We found that if the thickness of the thymus tissue is ≥1.095 cm, it can predict MIS-C with 70% sensitivity and 92.5% specificity. We found that if the volume of the thymus tissue is ≥9.915 cm3, it can predict MIS-C with 100% sensitivity and 58.5% specificity Finally, if the PLR level is ≥168.61, it can predict MIS-C with 90% sensitivity and 96.4% specificity (Table V). According to the risk analysis for the development of MIS-C in pediatric patients with COVID-19 infection, the risk of developing MIS-C increases by 40 times if the thymus transverse diameter is ≥4.030 cm, by 14.778 times if the thymus thickness is ≥1.095 cm, and by 40.5 times if the PLR value is ≥168.61 (Table V).

Discussion

To the best of our knowledge, our study is the only one in the literature to show that thymus tissue enlarged significantly in the MIS-C group. A higher amount of proinflammatory cytokines (TNFα, IL-1, IL-6) and chemokines were recorded in patients with severe COVID-19 symptoms compared to patients with mild

Table IV. Comparison of thymus sizes by age groups.

Thymus sizes	2-6 age (n=11)			P
	Control (n=5)	Covid-19 (n=5)	MIS-C (n=1)	
AP diameter	1.22±0.34	1.48±0.29	1.50±0.00	0.635
Transverse diameter	3.69±0.08	3.21±0.62	4.06±0.00	0.164
Length	2.19±0.27	2.14±0.42	2.40±0.00	0.540
Thickness	0.95±0.15	0.90±0.12	1.21±0.00	0.198
Volume	14.44±3.52	6.69±3.17	14.90±0.00	0.188
		7-13 age (n=21)		
	Control (n=7)	Covid-19 (n=7)	MIS-C (n=7)	P
AP diameter	1.07±0.13	1.66±0.26	1.45±0.22	0.001
Transverse diameter	3.89±0.28	3.56±0.68	4.89±0.900	0.012
Length	2.39±0.31	2.63±0.49	2.82±0.54	0.217
Thickness	0.94±0.13	0.98±0.15	1.11±0.08	0.035
Volume	13.12±2.12	13.86±4.57	14.64±4.13	0.872
		14-17 age (n=18)		
	Control (n=6)	Covid-19 (n=10)	MIS-C (n=2)	P
AP diameter	1.34±0.37	1.27±0.27	1.53±0.04	0.410
Transverse diameter	3.39±0.40	2.42±0.91	4.18±0.54	0.014
Length	2.24±0.49	1.70±0.56	3.14±1.02	0.042
Thickness	0.94±0.09	0.89±0.14	1.13±0.14	0.183
Volume	10.06±2.47	6.89±2.20	14.88±6.78	0.060

Independent-Samples Kruskal-Wallis Test

Table V. Determination of the best cut-off points of thymus dimensions and laboratory findings to predict MIS-C and risk analysis for MIS-C.

Variable	Cut off value	AUC	Sensitivity	Specificity	Asymptotic 95% confidence interval	P*
AP diameter	≥1.230	0.692	1.000	0.475	0.547-0.838	0.062
Transverse diameter	≥4.030	0.911	0.800	0.925	0.798-1.000	<0.001
Length	≥2.330	0.820	1.000	0.625	0.700-0.940	0.002
Thickness	≥1.095	0.876	0.700	0.925	0.760-0.992	<0.001
Volume	≥9.915	0.719	1.000	0.585	0.553-0.885	0.034
PLR	≥168.61	0.777	0.900	0.821	0.591-0.963	0.007
Risk analysis with logistic regression						
	Cut off value		OD	95% confidence interval		P**
Transverse diameter	≥4.030 cm		40	4.779-334.765		0.001
Thickness	≥1.095 cm		14.778	2.395-91.195		0.004
PLR	≥168.61		40.5	3.929-417.434		0.002

*ROC Curve analysis, **Logistic regression analysis
AP: anterior-posterior, AUC: area under curve, MIS-C: multisystem inflammatory syndrome, OD: odds ratio, PLR: platelet-lymphocyte ratio

symptoms Research reports that the lung findings in the pathogenesis of COVID-19 are associated with increased serum cytokine and chemokine levels.[16] Also, decreased lymphocyte count and increased neutrophil-lymphocyte ratio have been reported in patients with severe symptoms.[17,18] We suppose that the significant growth of the thymus tissue in cases with severe COVID-19 infection and MIS-C is due to increased cytokines and chemokines secondary to an overstimulated immune response. Additionally, although the lymphocyte count was lower in the MIS-C group compared to the other groups, there was no statistically significant difference. This insignificance may be due to the small number of cases. In the literature, lymphocyte deficiency in MIS-C cases has been tried to be explained by the direct lymphocyte attack against the virus and migration to tissue and inflammation areas in some studies.[19,20] In our study, NLR was significantly higher in the MIS-C group, consistent with the literature, and this increase was positively correlated with the transverse diameter, thickness, and length of the thymus tissue. We think that the reason for this significant increase in NLR and thymus tissue may be due to the increased cytokines and chemokines mentioned in the literature.[17] Scientists have investigated why children have been protected during the coronavirus outbreaks; they reported that less outdoor activity, less international travel, and low angiotensin-converting enzyme 2 (ACE2) receptor expression were the primary factors responsible in children.[21,22] After viral infections, antigen-presenting natural killer cells and macrophages present the antigenic structure of the pathogen to T cells and activate adaptive immunity. Adaptive immunity is responsible for the production of T helper cells, activation of antibodies, cytokines, chemokines, and elimination of infected cells. The adaptive immune system, of which the thymus is primarily responsible for, is the most effective system for preventing damage to the body by invading microorganisms.[5] The thymus is quite active in the intrauterine and neonatal period; it begins to shrink after birth and continues its effectiveness until puberty. With increasing age, the function and activity of the thymus decreases.[23,24] This condition is called immune aging. After immune aging, the individual becomes prone to infections, cancer, and autoimmune diseases.[25,26] Our study included the pediatric population. In our evaluation according to age groups, there was no significant difference between the groups in terms of thymus dimensions in the

2-6 age group. In the school period (7-13 years), thymus AP diameter was significantly higher in patients with COVID-19 than in the control group. In the MIS-C group, however, we found thymus transverse diameter and thickness to be significantly higher than both the control group and COVID-19 group. In the adolescence period, thymus transverse diameter and length were significantly higher in the MIS-C group compared to the other groups.

We did not observe a significant difference in thymus dimensions between cases with COVID-19 and MIS-C during the 2-6 age period, which is the lowest age group of the pediatric population in our study. The number of MIS-C cases with CT evaluation was low in this age group. However, the fact that childhood vaccinations, seasonal corona virus, and other viral infection exposures are high in this age group may cause thymus dimensions to be high in healthy children. Therefore, we think exposure to COVID-19 did not cause a sufficiently significant increase in thymus dimensions in this age group.

In our study, thymus transverse diameter and thymus thickness measurements in other age groups over 7 years of age were found to be significantly higher in all COVID-19 cases compared to the control group. Also, a significant increase in thymus dimensions was observed in cases diagnosed with MIS-C compared to COVID positive cases. We believe that as age increases, T cells become more sensitive to antigenic structures similar to coronavirus and as a result of this sensitization, COVID-19 triggers an irregular immune response.

The clinical-pathological examinations of patients infected with COVID-19 by Qin et al.[17] support this idea. This review highlights that tissue damage in COVID-19 patients is the result of a cytokine storm associated with a dysregulated immune response. The positive correlation between thymus dimensions (transverse diameter, thymus thickness, thymus length, and thymus volume) and CRP and/or NLR, which we found in our study, as well as the higher CRP, NLR, and procalcitonin levels in the MIS-C group support this. Çakmak et al.[18] reported a significant correlation between the severity of lung imaging findings and the platelet-lymphocyte ratios of COVID-19 patients and that decreased platelet and lymphocyte counts led to noticeable increases in imaging findings. For COVID-19 patients, the severity of imaging findings has been reported to be significantly correlated with the level of fat involution in the patients' thymus tissue. In our study, the platelet count was significantly lower in the MIS-C group. We also showed that if the PLR is ≥168.61, it can predict MIS-C with 90% sensitivity and 82.1% specificity. However, we did not find a significant correlation between PLT and PLR values and thymus volume. This may be due to the absence of pulmonary involvement in any of the pediatric patients included in our study, unlike the literature. Also, unlike the literature, we determined cut-off points for thymus dimensions to predict MIS-C in patients with COVID-19 infection. We determined that it can predict MIS-C with 91.1% sensitivity and 80% specificity, especially when the transverse diameter of the thymus is ≥4.030 cm. According to our risk analysis with logistic regression over this cut-off value, the risk of developing MIS-C increases by 40 times in patients with COVID-19 infection with a thymus transverse diameter of ≥4.030 cm, by 14.778 times if the thymus thickness is ≥1.095 cm, and by 40.5 times if PLR is ≥168.61.

The size of the thymus is known to decrease with X-rays. In fact, X-rays were used in the past years to reduce the size of the thymus, and when it was found to be carcinogenic, this form of treatment was avoided.[27] However, the fact that this is the only study in the literature that compares thymus dimensions and laboratory findings in age and sex-matched pediatric patients with COVID-19 infection makes our study valuable.

Our study shows that thymus dimensions and acute phase reactants are higher in pediatric patients in the MIS-C group. It also shows that thymus transverse diameter, thymus thickness, and PLR values pose a risk for the development of MIS-C. This supports the evidence that MIS-C emerges with a dysregulated immune response, due to excessive thymus activity against the COVID-19. However, it is still a matter of debate why the clinical course of COVID-19 varies from patient to patient. For this reason, there is a need for prospective studies with large participation, including genetic analyses, thymus dimensions, and cytokine levels.

Ethical approval

Ethical approval was obtained from the Ministry of Health and the local ethics committee of Kahramanmaras Sütcü İmam University before the study (Ethics committee date: 26.03.2021 Session: 2021/2022 Protocol no: 185 Decision no: 03).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SY, ŞG, AD; data collection: AD, NY, Sİ, UUG; analysis and interpretation of results: ŞG, AD, SY, UUG; draft manuscript preparation: AD, Sİ, NY, ŞG, All authors reviewed the results 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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