Relationship between Pneumonia and the Thymus Gland in Children with COVID-19: A Volumetric Computed Tomography Study

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J Pediatr Infect Dis 2022;17:33–39.

Abstract

Objective Many studies showed that less-severe disease symptoms and fewer mortality rates have been reported in pediatric novel coronavirus disease 2019 (COVID-19) patients. In this study, we aimed to reveal the relationship between the volume of thymus gland, which provides T lymphocyte maturation in children, with the severity of lung involvement and blood laboratory values in pediatric patients with COVID-19 infection.

Methods Thymus density and thymus and cardiac volumes were measured in pediatric COVID-19 patients and a control group that underwent thoracic tomography for reasons other than infection. Thymus/heart ratios were calculated to index the thymus volumes of the patients to their body dimensions. The severity of pneumonia was demonstrated by proportioning the involved lung parenchymal volume to the total lung volume in patients with typical involvement in thoracic tomography. The relationship between volumetric and blood laboratory values was statistically evaluated.

Results Thymus density ($p = 0.015$) and thymus/heart ratio ($p = 0.04$) significantly differed between patients with COVID-19 infection and the control group. A correlation was observed between the pneumonia involvement rate and C-reactive protein (CRP) (k: 0.451, $p = 0.08$) and white blood cell (WBC; k: 0.419, $p = 0.015$) values in the thoracic tomography of the COVID-19 group.

Conclusion The thymus gland is enlarged as an indicator of activation in COVID-19 infection. We hope that our study will guide new studies on the prognostic value of thymus size in lymphopenic patients with severe disease.

Keywords
- COVID-19
- pneumonia
- thymus
- computed tomography
- volumetric measurement

received
March 27, 2021
accepted after revision
September 21, 2021
published online
December 6, 2021

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1739392.
ISSN 1305-7707.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the new novel coronavirus disease 2019 (COVİD-19) as an epidemic which was first reported in Wuhan, China, as a pandemic.[1] It has been reported that the risk of children being infected with the pandemic agent COVİD-19 is equal to that of adults, but they mostly present as asymptomatic or with milder symptoms, and infected individuals are generally diagnosed as a result of screening a family contact. In publications to date, it is stated that pediatric cases that have contracted COVİD-19 have a better prognosis and shorter duration of hospitalization than adults, similar to the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) pandemics which are also members of the coronavirus family.[2,3]

According to the published data, children constitute approximately 1.2 to 5% of COVİD-19 cases and less than 1% of related hospitalizations.[4–6] The COVİD-19 infection has been reported to have a severe course (dyspnea, central cyanosis, and O_2 saturation < 92) in 5.2% of children, and critical (acute respiratory failure syndrome, encephalopathy, heart failure, coagulopathy, and acute renal failure) in 0.4%.[7] Several reasons have been suggested to explain why the COVİD-19 infection has a milder course in children compared with adults. The most important explanations are that angiotensin-converting enzyme 2, which is detected as the binding protein of COVİD-19, does not show sufficient maturation in children; repeated viral agent exposure in children can play a role in COVİD-19 immune defense; and the thymus gland, which plays an important role in the immune response, is active in children.[8,9]

The thymus is a lymphoepithelial organ that plays an important role in the maturation of the immune system and provides an environment for T lymphocyte differentiation and selection. In addition, B-cells are essential elements that contribute to the formation of protective immunity against pathogens, and the thymus contains an important subset of resident CD20 + B-cells.[10] It is known that plasma cells in the perivascular space in the thymus gland provide long-term protection against viruses by secreting antigen-specific antibodies. Studies have reported that the thymus gland develops antimicrobial immunity and specific T lymphocytes after local infection with some microbial agents.[11] In our study, we aimed to investigate the relationship between the thymus gland volume and severity of pneumonia and blood laboratory findings in COVİD-19 infected pediatric patients that underwent thoracic computed tomography (CT).

Materials and Methods

This retrospective study was approved by the Institutional Ethics Committee of Kütahya Health Sciences University (document date and number: July 20, 2020-E.6262). The case group consisted of patients who were found to be positive for COVİD-19 according to the reverse-transcription polymerase chain reaction (RT-PCR) test conducted at the Pediatric Department of Kütahya Health Sciences of University Evliya Çelebi Education and Research Hospital after March 11, 2020, when the World Health Organization (WHO) accepted COVİD-19 as a pandemic agent, as well as patients with a history of contact with infected people and typical radiological findings of COVİD-19 described in the literature. The typical radiological findings of COVİD-19 pneumonia were accepted as peripheral-bilateral ground-glass opacities, multifocal-round ground-glass opacities, inverted halo sign, and other findings of organized pneumonia.[12] In our study, thoracic CT examinations of patients infected with COVİD-19 were evaluated at the time of the diagnosis. Patients with a negative RT-PCR test and CT findings defined as atypical for COVİD-19 pneumonia in the thoracic CT examination and those with CT scans with insufficient diagnostic quality or unclearly defined thymus margins were excluded from the study. According to the anamnesis information obtained at the time of admission, the mean duration of symptoms was 2.4 days (1–4 days). The blood tests of the patients taken at the time of admission to the hospital were included in the study. All patients included in the study were pandemic pediatric service patients but no intensive care patients.

To determine the dimensional changes caused by the COVİD-19 infection in the thymus gland, patients who presented to the Emergency Service of Kütahya Health Sciences University Evliya Çelebi Education and Research Hospital Pediatric Department for noninfection reasons (e.g., traffic accident, assault, and fall from a height) and underwent thoracic CT before the pandemic between March and May 2019 were included in the control group. Similar to the case group, patients with thoracic CT scans with insufficient diagnostic quality and unclear thymus margins were excluded from the control group.

Thoracic CT examinations were performed with a 16-slice multidetector sequential CT scanner (Aquilion, Toshiba Medical Systems, Otawara, Japan). Images were acquired using window settings allowing the viewing of the lung parenchyma (window level, −500 to −700 Hounsfield's unit [HU]; window width, 1,200–1,500 HU) and the mediastinum (window level, 20–40 HU; window width, 350 HU). The thoracic CT examinations anatomically covered the area from the C1 vertebra to the bottom of the diaphragm. All patient CT examinations were noncontrast examinations.

The CT examinations of the case and control groups were uploaded from the hospital image archiving system to the workstation. The thymus (TV)-cardiac volumes (CV) of the cases and controls (►**Figs. 1–4**) and the volumes of the total lung and pneumonic involvement areas (ground glass and consolidation areas) in the case group (►**Fig. 5**) were calculated using the Vitrea FX version 6.1 (Vital Images Inc., a Canon Group Company, Minnetonka, Minnesota) software. Optimal volume measurements were undertaken with manual corrections where necessary. Thymus/cardiac ratios (TCR) were obtained by dividing TV by CV (TV/CV). In the case group, the severity of pneumonia was evaluated according to the pneumonia severity index (PSI) obtained by proportioning the ground glass opacity and consolidation areas to the total lung volume. The mean thymus density

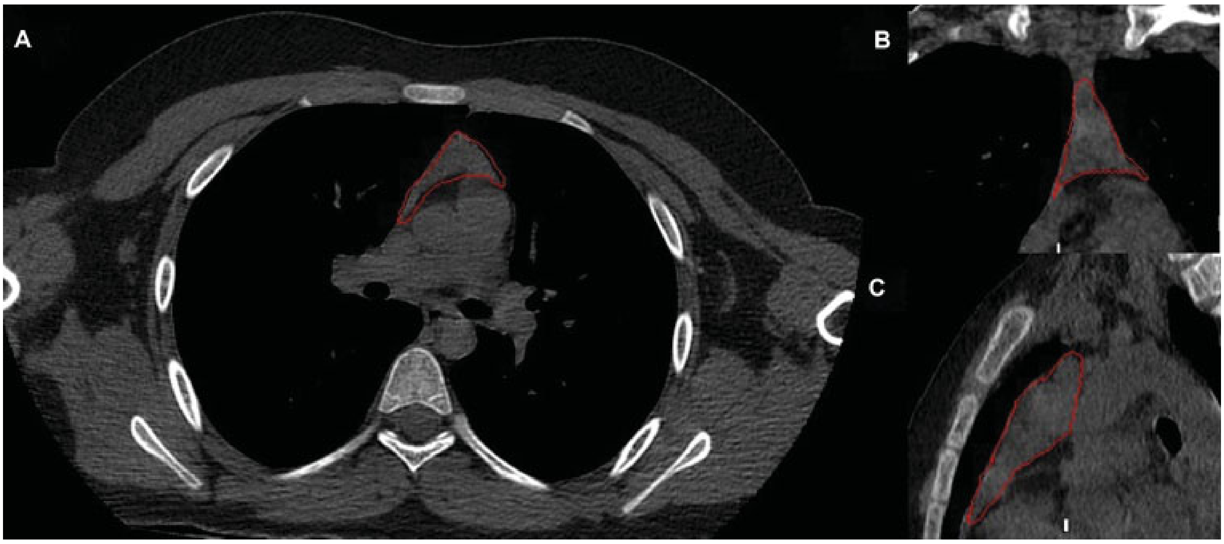

Fig. 1 Segmentation of the thymus gland in the axial (A), coronal (B), and sagittal (C) planes on noncontrast thoracic CT scans. CT, computed tomography.

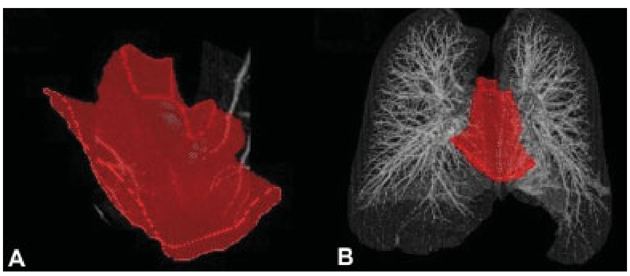

Fig. 2 3D image of the thymus gland in reformatted images (A and B). 3D, three-dimensional.

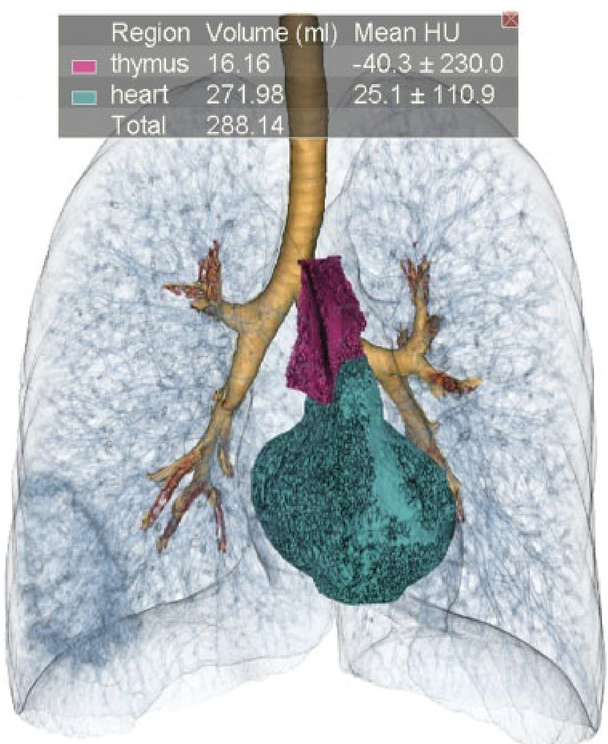

Fig. 4 3D image of the heart in reformatted images. 3D, three-dimensional.

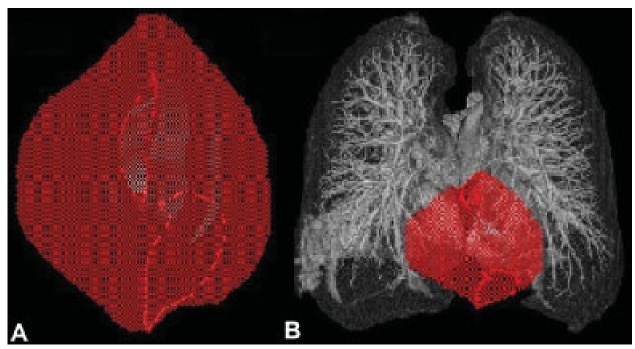

Fig. 3 Heart segmentation in the axial (A), coronal (B), and sagittal (C) planes on noncontrast thoracic CT scans. CT, computed tomography

(MTD) was measured in the axial plane where the thymus was the largest, with the region of interest (ROI) covering the thymus and recorded in HU.

The Statistical Package for the Social Sciences (IBM SPSS, version 21.0.0 for Windows) was used for statistical analyses. The conformance of the numerical dataset to normal distribution was determined by the Kolmogorov–Smirnov test. All data showed normal distribution. In the case group, the relationship between low O_2 saturation, fever, cough, loss of taste and smell, headache symptoms, and TV, TCR, and MTD was evaluated by independent-samples *t*-test. The relationship between TV, TCR, MTD and lymphocyte count and the case and control groups was evaluated using an independent-samples *t*-test. A *p*-value of <0.05 was considered to indicate a statistically significant difference.

In the case group, the relationships between PSI, the TV, TCR, and MTD volumetric values, blood parameters, namely, lymphocyte, white blood cell (WBC), C-reactive protein (CRP) were evaluated using Pearson's correlation test. The correlation coefficients were evaluated as follows: $r \geq 0.91$, excellent; $0.90 \geq r \geq 0.71$, good; $0.70 \geq r \geq 0.51$, moderate; $0.50 \geq r \geq 0.31$, weak; and $r \leq 0.3$, no correlation. In all analyses, $p < 0.05$ was considered as statistically significant.

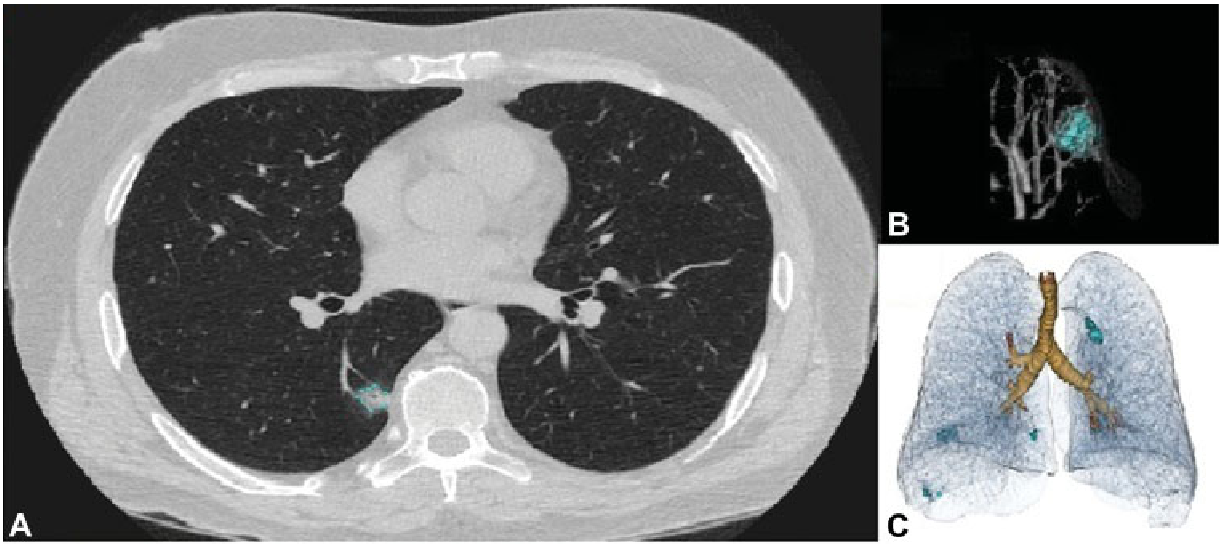

Fig. 5 (A-C) Software-supported automatic measurements of the thymus gland and cardiac volumes in reformatted images.

Results

The mean age was 12.4 ± 4.5 (minimum: 0.3, maximum: 17) years for the case group and 11.7 ± 4.2 (minimum: 0.1, maximum: 17) years for the control group, with no statistically significant difference. There were 19 (58%) boys and 14 (42%) girls in both groups. TV, MTD, and TCR were not related to gender. While TV and MTD were not associated with age, TCR decreased with age and showed a moderately significant inverse correlation with age (►**Table 1**).

Only two of the patients had O_2 saturation below 95% and they did not have tachypnea. In patients with low O_2 saturation, O_2 levels returned to normal with nasal O_2 and no additional intervention was required. Eight of the patients described decreased sense of taste and smell. There was cough in 22 patients, fever in 21 patients, and headache in 7 patients. There were no patients with gastrointestinal symptoms or skin rash. No significant correlation was found between the presence of symptoms and TV, TCR, MTD, and lymphocyte counts (►**Table 2**). The mean hospital stay of the patients was 3.1 (2–5) days.

In the independent-samples *t*-test performed between the case and control groups, the MTD and TCR values were found to significantly differ. In the COVİD-19 infected group, MTD was lower and TCR was higher. Although the TV value

Table 1 Pearson's correlation analysis of the relationship of TV, TCR, and MTD with age and gender

	Age	Gender
TV	r: 0.083, $p = 0.5$	r: -0.242 $p = 0.05$
TCR	r: -0.521, $p < 0.001$	r: 0.041 $p = 0.7$
MTD	r: -0.198, $p = 0.1$	r: 0.079 $p = 0.5$

Abbreviations: MTD, mean thymus density; TCR, thymus/cardiac ratio; TV, thymus volume.

Table 2 Independent samples *t*-test results of the mean TV, TCR, MTD values, lymphocyte counts, and clinical symptoms in the case group

	Fever			Cough			Loss of sense of taste and smell		
	+(n:22)	−(n:11)	*p*	+(n:21)	−(n:12)	*p*	+(n:8)	−(n:25)	*p*
TV	24.71 mL	22.21 mL	0.592	23.97 mL	23.71 mL	0.956	17.97 mL	25.76 mL	0.123
TCR	0.109	0.1	0.732	0.101	0.115	0.6	0.093	0.110	0.573
MTD	−20.88	−170.29	0.058	−27.72	−145.85	0.131	−41.80	−79.92	0.669
LC	2.16	2.28	0.641	2.17	2.25	0.743	2.39	2.14	0.375
	Low O_2 saturation				Headache				
	+(n:2)	−(n:31)		*p*	+(n:7)		−(n:26)		*p*
TV	19.50 mL	24.16 mL		0.614	17.98 mL		25.46 mL		0.159
TCR	0.170	0.102		0.190	0.125		0.101		0.419
MTD	45.60	−78.18		0.438	−2.87		−88.94		0.355
LC	2.64	2.17		0.367	2.44		2.13		0.302

Abbreviations: LC, lymphocyte count; MTD, mean thymus density; TCR, thymus/cardiac ratio; TV, thymus volume.

Table 3 Results of the independent-samples *t*-test of the mean TV, TCR, and MTD values and the lymphocyte counts of the case and control groups

	Case group	Control group	*p*-value
TV	23.87 mL	19.25 mL	0.09
TCR	0.1	0.07	0.04
MTD	−70.68 HU	23.35 HU	0.01
LC	2.42	2.07	0.36

Abbreviations: HU, Hounsfield's unit; LC, lymphocyte count; MTD, mean thymus density; TCR, thymus/cardiac ratio; TV, thymus volume.

was higher in the case group, it did not statistically significantly differ from the control group (►**Table 3**).

In the case group, there was no significant correlation between the presence of pneumonic involvement on thoracic CT and the TV, TCR, and MTD values. Among the COVİD-19 cases with pneumonic involvement, the relationships between PSI, TV, TCR, and MTD, and lymphocyte, WBC, and CRP values were evaluated with Pearson's correlation test and a moderately significant correlation was observed between the PSI and WBC and CRP values, but no correlation was determined between the remaining parameters (►**Table 4**).

Discussion

To the best of our knowledge, our study is the first to evaluate thymus gland sizes in patients with COVID-19, and it is important both in terms of its contribution to the literature and quantitative measurement of thymus size in thoracic CT examinations. In our study, the TCR and TV values in children infected with COVİD-19 were higher compared with the controls, and the increase in the TCR value was statistically significant. This finding can be considered as an indirect indicator of the active role of the thymus in COVID-19 infection. Most studies on the thymus gland, lymphocyte count, and immune system have been undertaken in HIV-infected cases. In studies conducted with HIV-infected cases, it was reported that the thymus gland volume was positively correlated with the CD4 lymphocyte count and negatively correlated with HIV viral load, and the thymus volume was suggested to guide lymphocyte activity. A dimensional increase in the thymus gland has been described in the CT measurements in HIV-infected patients with an increase in the number of CD4+ cells by >100 or more.[13] In the study of Varga et al, it was reported that lymphocytes count in the peripheral blood and thymus size showed a statistically significant positive correlation in newborns.[14] However, there are different mechanisms that affect the lymphocyte count in the peripheral blood independent of the thymus size in COVID-19 infection. CD8+ T-cells release perforin and granzyme A and B which induce apoptosis in virus-infected cells, chronic inflammatory state continuously stimulates T-cells and causes depletion of T-cells, and upregulation of NKG2A expression in inflammation leads to functional depletion of CD8+ and natural killer (NK) cells. These has been

Table 4 Pearson's correlation analysis of the relationship between PSI and volumetric and laboratory measurements

TV	*r*: -0.025, $p = 0.8$	LC	*r*: 0.157, $p = 0.3$
TCR	*r*: 0.233, $p = 0.1$	WBC	*r*: 0.419, $p = 0.01$
MTD	*r*: 0.183, $p = 0.3$	CRP	*r*: 0.451, $p = 0.01$

Abbreviations: LC, lymphocyte count; MTD, mean thymus density; PSI, pneumonia severity index; TCR, thymus/cardiac ratio; TV, thymus volume.

blamed for lymphopenia in COVID-19 infected patients.[15,16] It has been reported that increased secretion of proinflammatory cytokines, such as interleukin (IL)-1, interferon (IFN)-γ, and IL-6, to compensate for the maladministration of depleted lymphocytes plays a critical role in the induction of lymphopenia.[17] In addition, COVID-19 can directly target lymphocytes and destroy lymphoid organs. Since blood lactic acid levels are high in patients with severe COVID-19 infection, it has been reported that lymphopenia may be due to such metabolic causes.[18]

Lymphocytopenia has been reported at a rate of 3 to 3.5% in children infected with COVİD-19.[19,20] Lymphocytopenia is seen especially in elderly patients and severe cases of COVİD-19.[21–24] In a study by Liu et al, it was shown that the outflow of lymphocytes from the thymus was induced, which positively contributed to mortality in cases of lymphopenia that were given thymosin α 1 treatment.[25] In our study, lymphopenia was observed in only one patient (3%), and there was no significant correlation between the lymphocyte count and the TV and TCR values. There were no patients with severe COVID-19 infection findings in the patients included in the study. The lack of correlation between thymus volume and lymphocyte count in our study may indicate that similar lymphopenia mechanisms described also work in individuals who have mildly recovered from COVID-19 infection and the active role of the thymus in patients with lymphopenia. In our study, the amount of lymphocytes in the COVID-19 infected patient group did not differ significantly with the control group.

The thymus is quite active in the intrauterine and neonatal period and begins to decrease partially after birth but continues to be active until puberty.[26] In the study of Varga et al, it was proved that there is a statistically significant positive correlation between thymus size and body size in newborns.[14] In our study, we included TCR in addition to TV to provide standardization between body dimensions and thymus volume. When we evaluated the control and patient groups together, we found that TCR showed a negative correlation with age but studies with larger patient groups including adults are needed to determine whether this is secondary to the increase in heart size with increasing age. Our study was conducted on pediatric patients under the age of 18 years, and no significant relationship was found between TV and age, probably because the difference between age groups was limited or because our patient and control groups were small. In our study, the MTD value was found to be significantly lower in cases compared with the control group which was considered to be related to gland activation. However, since there is no similar research in the literature, further studies are needed to support our findings.

In the literature, abnormal thoracic CT findings have been described in 60 to 80% of children infected with COVİD-19.[2,27,28] In our study, pneumonic infiltration was detected in the 52% of the cases. To determine the severity of pneumonia involvement, we compared the volume of ground-glass opacity and consolidation areas to the total lung parenchyma volume (PSI). While PSI did not correlate with the TCR and lymphocyte values, it was correlated with CRP and leukocyte count. In a study conducted by Garcia-Vidal et al with COVİD-19 cases followed-up in hospital, the presence of a microbiologically confirmed secondary infection agent was revealed in 7.2% of the patients.[29] In another study, Fattorini et al proved the presence of bacterial superinfection in 11.7% of the cases.[30] It was considered that the correlation of the PSI value with leukocyte count and CRP might be an indicator of concomitant bacterial superinfection, especially in severe patients with lung involvement. However, in our study, there was no patient with a microbiologically confirmed bacterial superinfection. In addition, broad-spectrum antibiotics were routinely included in the treatment of all patients with lung infiltration.

Conclusion

Thymus gland is enlarged in COVİD-19 infected children as an indicator of the activation of the virus. While thymus gland sizes are an indicator of the amount of lymphocytes in the peripheral blood in healthy individuals and during the treatment of some diseases (HIV-infected patients), we could not find a similar correlation with the susceptibility to lymphopenia in COVİD-19 infection. Prospective studies with larger case series are needed to elucidate the effect of the thymus gland on the milder course of COVİD-19 infection in children and to guide new treatment strategies.

Conflict of Interest
None declared.

References

1 WHO Director-General's opening remarks at the media briefing on COVID19 -March 2020. Accessed October 4, 2021 at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—1/211-march-2020

2 Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. Pediatr Pulmonol 2020;55(05):1169–1174

3 Rehman S, Majeed T, Azam Ansari M, Ali U, Sabit H, Al-Suhaimi EA. Current scenario of COVID-19 in pediatric age group and physiology of immune and thymus response. Saudi J Biol Sci 2020; 27:2567–2573

4 Bialek S, Boundy E, Bowen V, et al; CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. Morb Mortal Wkly Rep 2020;69(12):343–346

5 Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020 [in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi 2020;41(02):145–151

6 Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA 2020;323(14):1335

7 Dong Y, Mo XI, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics 2020;16:16

8 Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020; 367(6483):1260–1263

9 Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020;109(06):1088–1095

10 Spencer J, Choy M, Hussell T, Papadaki L, Kington JP, Isaacson PG. Properties of human thymic B cells. Immunology 1992;75(04): 596–600

11 Nuñez S, Moore C, Gao B, et al. The human thymus perivascular space is a functional niche for viral-specific plasma cells. Sci Immunol 2016;1(06):eaah4447

12 de Jaegere TMH, Krdzalic J, Fasen BACM, Kwee RM. COVID-19 CT Investigators South-East Netherlands (CISEN) study group. Radiological Society of North America Chest CT Classification System for Reporting COVID-19 Pneumonia: Interobserver Variability and Correlation with Reverse-Transcription Polymerase Chain Reaction. Radiol Cardiothorac Imaging 2020;2(03): e200213

13 Rubio A, Martínez-Moya M, Leal M, et al. Changes in thymus volume in adult HIV-infected patients under HAART: correlation with the T-cell repopulation. Clin Exp Immunol 2002;130(01): 121–126

14 Varga I, Toth F, Uhrinova A, Nescakova E, Polak S. Association among size of thymus, anthropometric dimensions and number of lymphocytes in peripheral blood in newborns from Slovakia. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2009; 153(03):229–234

15 Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med 2020;26(04):453–455

16 Fathi N, Rezaei N. Lymphopenia in COVID-19: therapeutic opportunities. Cell Biol Int 2020;44(09):1792–1797

17 Jeffery LE, Burke F, Mura M, et al. 1,25-dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J Immunol 2009;183(09):5458–5467

18 Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020;5(01):33

19 Lu X, Zhang L, Du H, et al; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 infection in children. N Engl J Med 2020; 382(17):1663–1665

20 Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med 2020;58(07):1135–1138

21 Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020;11(827):827

22 Huang PC, Wang Y, Li PX, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395 (10223):P497–P506

23 Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(07):1730–1741

24 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061–1069

25 Liu Y, Pang Y, Hu Z, et al. Thymosin alpha 1 (Tα1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells. Clin Infect Dis 2020;x:630
26 Güneş H, Dinçer S, Acıpayam C, Yurttutan S, Özkars MY. What chances do children have against COVID-19? Is the answer hidden within the thymus?. Eur J Pediatr 2021;180(03):983–986
27 Yang P, Liu P, Li D, Zhao D. Corona virus disease 2019, a growing threat to children? J Infect 2020;80(06):671–693
28 Liu H, Liu F, Li J, Zhang T, Wang D, Lan W. Clinical and CT imaging features of the COVID-19 pneumonia: focus on pregnant women and children. J Infect 2020;80(05):e7–e13
29 Garcia-Vidal C, Sanjuan G, Moreno-Garcia E, et al; COVID-19 Researchers Group. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 2021;27(01):83–88
30 Fattorini L, Creti R, Palma C, Pantosti AUnit of Antibiotic Resistance and Special Pathogens Unit of Antibiotic Resistance and Special Pathogens of the Department of Infectious Diseases, Istituto Superiore di Sanità, Rome. Bacterial coinfections in COVID-19: an underestimated adversary. Ann Ist Super Sanita 2020;56(03):359–364

