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Radiological changes in the thymus in patients who have had COVID-19 and in vaccinated persons who have not had COVID-19: a CT study

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Abstract

Background: There are very few and limited studies on the role of the thymus in COVID-19 infection. It is known that thymus morphology changes in individuals vaccinated against COVID-19 although they do not have active infection.
Objective: Our study aims to evaluate these differences in detail.
Methods: This research was conducted in a total of 141 people, 75 women and 66 men. The research consisted of three groups: unvaccinated persons who have had the disease ($n = 49$), vaccinated persons who have not had the disease ($n = 37$), and unvaccinated persons who have not had the disease (control group, $n = 55$). In the study, the thymus volume, structure, and fat content were investigated and the differences between groups were evaluated.
Results: Thymus volume was greatest (0.43 ± 0.11) in the vaccinated group that had not had the disease and smallest (0.15 ± 0.07) in the unvaccinated group that had had the disease, and a significant difference was found between the groups. Thymus steatosis was seen mostly in the unvaccinated group that had had the disease (72%; $p = 0.04$). The diffuse nodular pattern was only present in the diseased group.
Conclusion: This research is the first study in the literature to date on the effect of COVID-19 and vaccines on the thymus. In addition to the acute consequences of the virus, the possibility of negative symptoms after COVID-19 should also be kept in mind, especially in unvaccinated people. Further studies are needed to confirm the results reported herein.

Keywords
Thymus · COVID-19 · Vaccination · Morphology · Computerized Tomography

Introduction

Coronavirus 2 (SARS-CoV-2) is a new pathogen that causes excessive production of proinflammatory cytokines, leading to acute respiratory distress syndrome [1]. As with many viral infections, the acute phase of SARS-CoV-2 infection is characterized by more or less severe lymphopenia in symptomatic patients [1]. In many infected people, it causes lung inflammation or, in more severe cases, severe pneumonia that requires hospitalization in intensive care units. Despite intensive care, fatal outcomes occur in 6 and 12%, respectively, of women and men over 80 years of age who are hospitalized with severe COVID-19 [2]. According to data of the Ministry of Health in Turkey, the lowest death rate is in the 15–24 years age group with 0.03%, while the highest death rate is in the 80 years and over age group with 26.94% [3]. Factors associated with a higher risk of death in patients

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with SARS-CoV-2 include age and low circulating lymphocyte counts [4].

The thymus is a primary lymphoid organ, the site of T cell development, and the source of mature T cells. Beginning in adolescence, the thymus begins to shrink in a process called thymic involution [5]. As a result of this phenomenon, an individual's ability to respond to new pathogens decreases. In March 2020, radiologists at the Clinique Ambroise Paré in Neuilly analyzed chest CT scans of patients hospitalized in the intensive care unit with COVID-19-related acute respiratory distress syndrome, observing that most exhibited thymic hyperplasia. They stated that thymus density appears to be associated with greater lung damage but also with a better prognosis. Following this observation, researchers have shown that in approximately 20% of patients, thymic function was greater than in control subjects hospitalized in the same intensive care unit, regardless of the age of the patients [6]. Severe lymphopenia is frequently observed in severe COVID-19 patients, and both phenotypic and functional changes in antiviral T cells have been associated with the severity of COVID-19 [2]. The thymus, the organ that produces T lymphocytes, undergoes progressive physiological involution with age. However, rare cases of thymic hyperplasia are reported in the elderly as well as in patients with autoimmune diseases or cancer. Thymic hyperplasia is observed in response to profound lymphopenia, whether or not associated with sepsis [4].

There are very few and limited studies on the role of the thymus in COVID-19 patients. In these studies, morphological differences that occurred along with functional changes in the thymus were also brought to the agenda. It is known that thymus morphology changes in individuals vaccinated against COVID-19, although they do not have active infection [4]. The aim of this study is to investigate the possible changes in thymus morphology caused by COVID-19 infection and vaccination.

Methods

Research design

This retrospective study was conducted in our imaging center with patients over 18 years of age who had undergone a thoracic CT examination between January 2017 and August 2022.

Ethics

The study was carried out with the permission of the Istanbul Medipol University Hospital Ethics Committee (decision no.: BTEDK-2022/9). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki. Consent was obtained from the patients.

Population and sample

Power analysis was performed using the G*Power (v3.1.9.7, Heinrich Heine University Düsseldorf, Germany) program to determine the number of samples. The power of the study is expressed as $1-\beta$ (β = type II error probability). In the calculation, the effect size (d) was found to be 0.36 to obtain 80% power at $\alpha = 0.05$. Accordingly, it was calculated that groups in the study should consist of at least 35 people. The research was conducted with a total of 141 persons. The age range of the participants was 20–55 years. There were 12 people between the ages of 20 and 27, 13 people between the ages of 28 and 32, 31 people between the ages of 33 and 40, 36 people between the ages of 41 and 47, and 49 people between the ages of 48 and 55.

Inclusion criteria

Patients between the ages of 15 and 85 years who did not have any thoracic trauma, pneumothorax, lung disease, etc. were included in the study.

Exclusion criteria

Patients with examinations that contain low-quality images with noise and scattering (beam scattering), images that contain patient or device-related errors during shooting, and images with the desired areas not within the image area were excluded. Patients who had trauma to the thorax area, who had tumor formation in the areas to be examined, or who had undergone surgery were not included in the study.

CT protocol

Images taken in the axial plane with a 32-detector multi-slice CT device with a section thickness of 0.625 mm were used.

Research groups

The research consists of three groups.

First group

Previous disease and unvaccinated patients who had clinical and radiological signs of the disease and whose infection was proven by laboratory tests. In the first group, 35% of the patients were hospitalized, 65% were outpatients, and there were no patients in intensive care. Following the realization that PCR tests during the COVID-19 pandemic frequently yielded false-negative results, chest computed tomography (CT) was performed on almost every patient who presented with suspected COVID-19 based on clinical examination and laboratory findings. Thoracic CT examination was performed in almost every patient with suspected COVID-19 findings. The inpatient group was excluded from the study because many of them had comorbidities. These patients were not included in the study to prevent additional diseases from affecting our study results. In outpatients, there were signs of acute- and subacute-phase COVID-19 infection in the form of mild and moderate lung involvement. Repeated control CT scans were performed in this patient group during the treatment process, but control scans were not included in our study.

Second group

Vaccinated with no disease patients were subjects who had completed the primary series of vaccination with two doses of the BNT162b2 Pfizer–BioNTech vaccine. Individuals with clinical suspicion of lower respiratory tract infection and who had no evidence of the disease in CT scans and enzyme-linked immunosorbent assay (ELISA) tests were included in this group.

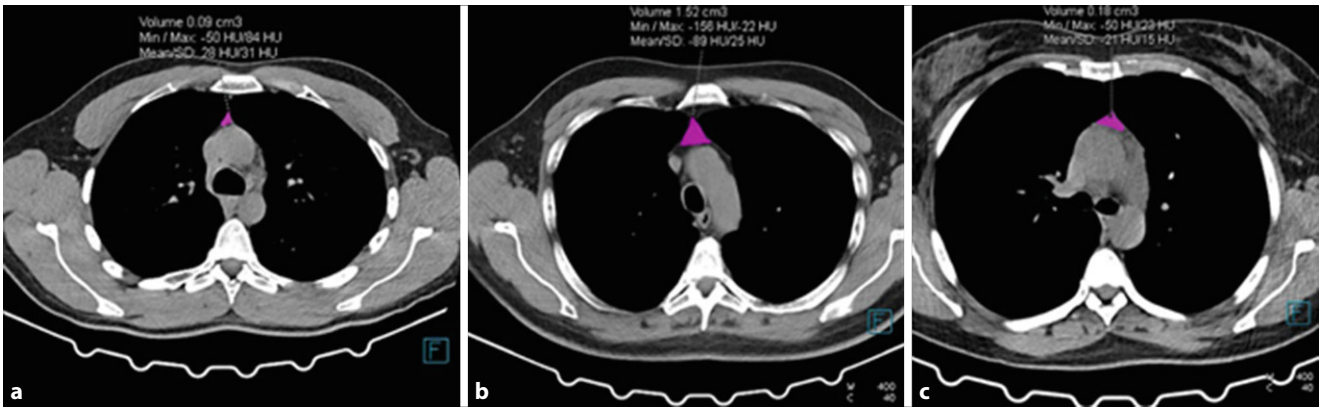

Fig. 1 ▲ Thymus volume measurement according to groups. **a** Experienced disease, unvaccinated—group I, **b** no disease, vaccinated—group II, **c** no disease, unvaccinated—group III

All vaccinated patients who did not have the disease were subjected to a CT scan with suspicion of COVID-19 and were examined in clinics and laboratories. These were patients whose diagnosis of COVID-19 was excluded by evaluating them together with their findings. Also biochemistry lab. When evaluated together with the findings, low-dose thoracic CT scans were performed on patients who were not diagnosed with COVID-19 but who had high concerns about it. There were also examinations performed due to the sense of panic and obsession that both the healthy patient population and the healthcare team felt in the early days of the COVID-19 pandemic.

Third group

Disease-free, unvaccinated control group, for which it was accepted that the disease did not spread to our country before 2019. Images of patients who underwent thoracic CT for various reasons and who could be used as a control group in terms of age and image quality and without any signs of mass or infection were included. Thoracic CT scans taken for various indications in our institution before 2019 were retrospectively scanned, and thymus volume measurements and patterns were recorded. In this group, patients with comorbidities or viral pneumonia were excluded from the study.

Research parameters

Thymus volume, density/types (types 1–4), patterns (diffuse reticular, diffuse nodular, nodular), and steatosis rate were measured, and comparisons were made between groups. The acquired data were later processed at a workstation in axial plane and volume rendering technique (VRT) format to acquire volumetric and subvolumetric images. Morphological and morphometrical analyses of the thymus were performed on axial images (**Fig. 1**).

Analyses

The quantitative parameters were measured manually using the RadiAnt DICOM Viewer 2023.1 for the study groups. All measurements were made by two radiologists at different times and independently of each other. The study examined intra- and interobserver agreement by calculating Cohen's kappa coefficient and the intraclass correlation coefficient. Interobserver agreement was analyzed as 89%. Statistical analyses were carried out using the SPSS for Windows statistical package (version 21.0; IBM Corp., Armonk, NY, USA), and a *P*-value < 0.05 was considered significant.

Results

It was determined that of the individuals participating in the study, 53.2% ($n = 75$) were female and 46.8% ($n = 66$) were male. The average age was 48.68 ± 16.09 years. While 39.7% ($n = 56$) of the participants were under the age of 40, 60.3% were over the age of 40. It was determined that 34.8% ($n = 49$) of the participants had had the disease (group I), 26.2% ($n = 37$) had not had the disease but were vaccinated (group II), and 39% ($n = 55$) had not had the disease and were unvaccinated (group III; **Table 1**).

It was determined that the thymus volume was highest in group II, i.e., in the vaccinated group that had not had the disease, and lowest in the unvaccinated group that had had the disease, and group I showed statistical significance with the other groups ($p < 0.05$; **Table 2**).

It was determined that differences in thymus density ($p = 0.564$) were not significant between the groups ($p > 0.05$; **Table 2**).

It was determined that thymus volume differed according to age and was higher in people older than 40 years ($p < 0.05$).

While it was determined that 65% of the people in the unvaccinated group who had not had the disease (group III) had 25% steatosis, 75% steatosis was seen mostly in the unvaccinated group who had had the disease (group I; 72%; $p = 0.04$). It was determined that the diffuse nodular pattern was only observed in unvaccinated individuals who had had the disease (group I; **Table 3**).

Discussion

Compared to other coronavirus infections, a hyperimmune response is evident in SARS-CoV-2 infections, and this contributes to the severity of the disease [7]. Elevated levels of inflammatory cytokines, particularly interleukin (IL)-6, IL-1, and IL-10, have been observed in COVID-19 patients [8]. Moreover, cytokine levels are

Table 1 General characteristics of the participants

		Frequency	Percent
Gender	Female	75	53.2
	Male	66	46.8
Age	< 40 years	56	39.7
	> 40 years	85	60.3
Group	Experienced disease, unvaccinated; group I	49	34.8
	No disease vaccinated; group II	37	26.2
	No disease, unvaccinated; group III	55	39.0

inversely proportional to CD4 and CD8 T cell numbers, seen as lymphopenia in peripheral blood, and this delayed immune response underlies the hyperinflammatory syndrome in COVID-19 [9]. Therefore, the best-known pathophysiology of COVID-19 is hyperinflammation and a cytokine storm as an immune response [10, 11]. Viral, bacterial, parasitic, or fungal infections are associated with pathological thymic atrophy. In particular, the thymus is one of the target organs of viruses. Infection caused by SARS-CoV-2, among others, causes thymic atrophy through direct or indirect mechanisms [9]. However, to our knowledge, there is no report documenting the effect of vaccines against this virus on the thymus. In this study, we determined that in line with the literature, the thymus volume was highest in the vaccinated group without the disease and lowest in the unvaccinated group with the disease. The fact that the thymus volume is highest in group II shows that the vaccine increases the thymus volume. In addition to the volume-reducing effect of the disease due to the minimum thymus volume in group I, it can also be thought that the symptoms of the disease requiring hospital admission occur more intensely in people with a low thymus volume.

Patients in group I in our study had had fever, cough, shortness of breath, muscle aches, headache, loss of taste or smell, sore throat, and general weakness. The general health condition of individuals in group II was good. Individuals in group III had had cold-like symptoms. Additionally, antiviral drugs, corticosteroids, anticoagulants, and other drugs can be used to treat the disease. Depending on the severity of the disease, antibiotics may also be required. One of the reasons why we did not include the inpatient group in our patient collective was that these patients were administered cortisone and similar drugs, and we thought that these might have had an effect on the thymus volume and pattern.

In a study conducted in the babies of mothers who had and had not had COVID-19, it was stated that the size of the thymus decreased in pregnant women and their babies with mild or moderate symptoms after recovering from the infection [12]. However, in another study conducted by the same researchers, it was stated that there were no differences in thymus sizes when individuals in the acute phase of the infection were compared with the healthy group [13]. Cuvelier et al. [6], who investigated protective reactive thymus hyperplasia in COVID-19 acute respiratory distress syndrome, stated that thymus enlargement is frequently seen in COVID-19 patients and that this condition is associated with increased T lymphocyte production, which seems to be a beneficial adaptation to virus-induced lymphopenia. It was also emphasized that a lack of thymic activity/reactivation in elderly SARS-CoV-2-infected patients may contribute to a worse prognosis. Although thymus hyperplasia was mentioned in the latter study, it was not stated whether the patients were vaccinated or not. We think that the higher thymus volume in the vaccinated group without the disease in our study compared to the other groups is due to the vaccine increasing thymic activity. Additionally, studies have indicated that the pathology behind this involution can be explained by hypothalamic–pituitary–adrenal axis activation and lymphocyte migration towards the affected organs, and these situations may result from corticomedullary reduction in the thymus [14, 15].

The results of Baron et al.'s [16] study of normal CT scans of the mediastinum show that thymus size decreases after puberty, a phenomenon well known to anatomists and pathologists. T lymphocyte production declines again around age 40–50 years, when the rest of the thymus degenerates further. This secondary atrophy causes the production of naive T cells to decrease significantly. In addition, lymph nodes become insufficient to store, maintain, and support immature T cells with advancing age. As a result, there is a decrease in the attenuation value in elderly patients, and these changes lead to results consistent with fat replacement [17]. Baron et al. [16], whose data correlate well with findings from previous autopsy studies, found that according to such studies, the maximum weight of the thymus occurs at age 12–19 years. It has been emphasized that between the ages of 20 and 60, a decrease in size occurs with fat tissue replacement. Aging-associated immunity describes age-related changes in both the innate and adaptive immune systems that lead to a decreased ability to fight new infections and contributes to the development of chronic infection. These changes in the immune system lead to higher infection rates [18]. Considering that COVID-19 also has a higher prevalence in older individuals, it is not surprising that the thymus volume was lower in people over 40 years of age in our study. In adolescence, there is a 90% decrease in T cell production through involution of the thymus, which turns into fatty tissue [19]. It has been reported that T lymphocyte production decreases again at the age of 40–50 when the rest of the thymus degenerates further [19]. It is thought that the changes observed in immunosenescence may not be caused by a decrease in immune cells, but rather by a more complex change of effects in various immune responses [20, 21]. In our study, it was determined that thymus density did not differ between the groups.

Although it has been observed that there is a decrease in the number of B, T, T helper, and natural killer lymphocytes in SARS-CoV-2 patients, humoral immunity and antibody production have a very important role in protecting the body against viruses and preventing the recurrence of

Table 2 Change in thymus volume according to groups

Group		Volume			Density and concentration		
	N	min	Mean ± max	*p*-value	min	Mean ± max	*p*-value
Experienced disease, unvaccinated; group I	49	0.02–1.157	0.157 ± 0.07	0.002, I–III, I–II	−80.00–29.00	−28.20 ± 23.22	0.564
No disease vaccinated; group II	39	0.01–2.07	0.438 ± 1.10		−106.00–58.00	−29.78 ± 32.05	
No disease, unvaccinated; group III	54	0.01–1.64	0.298 ± 0.09		−89.00–56.00	−19.14 ± 35.66	

Kruskal–Wallis test, post hoc test, $p < 0.057$

Table 3 Distribution of adiposity rate and pattern by groups

			Group			Total
			Experienced disease, unvaccinated; group I	No disease vaccinated; group II	No disease, unvaccinated; group III	
Adiposity rate	25%	*N*	12_a	2_a	26_b	40
		%	30.0%	5.0%	65.0%	100.0%
	25–50%	*N*	10_a	5_a	4_a	19
		%	52.6%	26.3%	21.1%	100.0%
	50–75%	*N*	8_a	8_a	10_a	26
		%	30.8%	30.8%	38.5%	100.0%
	75%	*N*	18_a	$3_{a,b}$	4_b	25
		%	72.0%	12.0%	16.0%	100.0%
	75–100%	*N*	0_a	0_a	2_a	2
		%	0.0%	0.0%	100.0%	100.0%
	100%	*N*	1_a	$1_{a,b}$	9_b	11
		%	9.1%	9.1%	81.8%	100.0%
Pattern	DR	*N*	32_a	30_a	38_a	100
		%	32.0%	30.0%	38.0%	100.0%
	DN	*N*	6_a	$0_{a,b}$	0_b	6
		%	100.0%	0.0%	0.0%	100.0%
	N	*N*	11_a	7_a	16_a	34
		%	32.4%	20.6%	47.1%	100.0%

Chi-square. Each subscript letter denotes a subset of group categories whose column proportions do not differ significantly from each other at the 0.05 level
DR diffuse reticular, *DN* diffuse nodular, *N* nodular

viral diseases in the future. However, an increased thymus volume has been reported to be associated with increased T lymphocyte formation in COVID-19-infected individuals, a beneficial adaptation to COVID-19-induced lymphopenia [22]. Loss of this thymic role in elderly SARS-CoV-2 patients may lead to worse outcomes [23]. Cytokine storms can also cause death in chronic cases. Acute pathology in severe cases of SARS-CoV-2 is the result of a powerful cytokine storm. The late interferon response weakens the adaptive immune response by causing the virus to replicate to evade the host antiviral reaction, resulting in impaired thymus activity. One of the most striking results of our research is that the least fatness in the thymus (25%) was observed in unvaccinated individuals who had not had the disease, and the most fatness (75%) was detected in unvaccinated individuals who had had the disease. The reason for this may be that the thymus is more atrophied in the group with the experienced disease, or it may be that the rate of infection is higher in those who previously had a lot of fatty thymus tissue. As a matter of fact, this group is the group with the least volume. Tresckow et al. [24] demonstrated that thymic hyperplasia following mRNA-based COVID-19 vaccination can occur not only in regional lymph nodes but also in the thymus. Since such a condition associated with COVID-19 may suggest that the treatment of cancer patients is inadequate, it is extremely important to distinguish possible immune responses from malignancy involvement to avoid false-positive staging results. When evaluated together with the increase in disease and hospital admissions in older ages and the data on volume decrease over the age of 40, this issue should be studied in large series. In a study investigating thymus morphology with CT in healthy individuals, it was reported that a large percentage of older patients had a low-density thymus, and in most patients over the age of 40, the thymus volume decreased and adiposity increased [25]. When the infection and the vaccine developed against this virus are evaluated together, it is expected that the most steatosis will occur in unvaccinated individuals who have had the disease, and that the thymus volume will decrease in those over 40 years of age. Not only the acute viral effects of SARS-CoV-2 but also post-infection events in vaccinated and unvaccinated individuals are becoming more important and challenging in the management of patients.

The main strength of this study was its innovative and forward-looking design. The main limitations were the history of hospitalization and intensive care among those who had had the disease, the time since the disease or vaccination, and the lack of significant numbers of participants in all groups. Furthermore, vaccinated persons who had had the disease were excluded, the study was conducted in a single center, and CT scans were performed at a wide time interval (24 days–6 weeks).

As a result, the thymus volume was highest in the vaccinated group that had not had the disease and was lowest in the unvaccinated group that had had the disease. This research is the first compre-

hensive study in the literature to date on the effect of SARS-CoV-2 and the vaccine on the thymus. In addition to the acute consequences of the virus, the possibility of negative symptoms after COVID-19 should also be kept in mind, especially in unvaccinated persons. Further studies are needed to confirm the results reported herein.

The purpose of the study was to question the relationship between disease and vaccination, not treatment. It is recommended to study whether thymus changes are temporary or permanent, to assess the severity of the disease, and to examine the relationship to the treatment strategy, etc., in the future.

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Data availability. Due to the protection of participants' confidentiality, the data are not presented explicitly. However, they can be shared upon request.

Declarations

Conflict of interest. B.T. Demir, M.R.M. Söğütlügil, and F. Çankal declare that they have no competing interests.

All procedures performed in studies involving human participants or on human tissue were carried out with the permission of Istanbul Medipol University Ethics Committee (decision no.: BTEDK-2022/9) and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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