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Evaluation of the relationship between the presence of thymus gland and COVID-19 pneumonia in adult patients

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Abstract. – OBJECTIVE: There is a direct correlation between age and COVID-19 mortality. Some researchers have suggested that this may be related to the loss of volume and function of the thymus gland with age. We aimed at investigating the relationship between the presence of the thymus gland and the severity of coronavirus diseases (COVID-19) pneumonia in adult patients.

PATIENTS AND METHODS: Between May 2020 and May 2021, adult patients aged 20-60 years old who had been admitted to the emergency department and had a positive SARS-CoV-2 polymerase chain reaction (PCR) test were included in the retrospective study.

RESULTS: The study reviewed a total of 465 patients, including 186 (40%) female, and 279 (60%) male patients. The mean age of patients was 40.46±12.18 years (range, 20-60). Pneumonia was detected in 281 (60.4%) of 465 patients. Of the total, 260 (55.9%) patients were detected with the thymus. Pneumonia was 3.85 times more common in patients without a thymus. The mean number of infected lung segments was 4.84 times higher in patients without a thymus. A negative correlation of -0.639 was found between the presence of the thymus and pneumonia.

CONCLUSIONS: For COVID-19 patients, there is a statistically significant correlation between the severity of lung findings on thorax CT examination and the level of involution in the patients' thymus tissue. The presence of the thymus may be a good preventative for pneumonia.

Key Words:
COVID-19, Pneumonia, SARS-CoV-2, Thymus.

Introduction

The new type of coronavirus pandemic, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been seriously affecting human health. While SARS-CoV-2 infection is less symptomatic and less common in children, it has been found to be more symptomatic and more fetal in adults[1].

Why are adults more affected by Coronavirus disease 2019 (COVID-19) infection, while children are less affected? People who develop comorbidities are known to be at higher risk for severe COVID-19 infection. However, age is also an important risk factor among those who do not have comorbidities. There is a direct correlation between age and COVID-19 severity and mortality[2]. Some researchers have suggested that this condition may be related to the loss of volume and function of the thymus gland with age[1-3].

As far as we know, there are very few publications about the relationship between the presence of the thymus gland and COVID-19 pneumonia.

Our aim in this study was to evaluate whether there is an association between COVID-19 pneumonia and thymus gland presence after decoupling adult patients with a positive SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) test by age group.

Patients and Methods

This study was designed as a retrospective, single-center clinical study. It was approved by the Institutional Ethics Committee of Malatya Turgut Ozal University (document date and number: 03.08.2021, 2021/52). The study protocol complied with the ethical guidelines of the Declaration of Helsinki of the World Medical Association.

The data will be collected through the hospital information system. The age, gender, PCR test results, and computed tomography (CT) of the patients will be examined from the patient files.

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Patients

Patients admitted to the Emergency Outpatient Clinic of the Malatya Turgut Ozal University, between May 2020 and May 2021 were included in the study. Patients who were found to be positive for COVID-19 according to the real-time RT-PCR test and had a thoracic CT scan were included in the study.

Patients with insufficient diagnostic quality or unclearly defined thymus margins and CT findings defined as atypical for COVID-19 pneumonia in the thoracic CT examination and a negative real-time RT-PCR test were excluded from the study. Patients with hematological or oncological disease and interstitial lung diseases were also excluded from the study.

Thoracic CT Scans

Philips Ingenuity CT, 2014, 128 slices, serial No. 600021 (Philips Healthcare, The Netherlands). Philips MX, 2014, 16 slices, serial No. EP16E140004 (Philips Healthcare, The Netherlands).

The categories of CO-RADS were used for diagnosis and classification[4].

The thymus gland was classified according to the attenuation of the parenchyma by examining the CT of the thorax[5]. Grade 0: Thymus in normal soft tissue density (Figure 1); Grade 1: Thymus with less than 50% fat content (Figure 2); Grade 2: More than 50% greasiness (Figure 3); Grade 3: Complete fatty degeneration (Figure 4).

Statistical Analysis

The numerical figures obtained from the measurements are expressed as mean±standard deviation, and the data obtained by counting are expressed as frequencies (%). The Student's *t*-test was used in analyzing the significance between the groups. The prevalence of the above was evaluated using the Fisher's exact test. One-way ANOVA was used to determine whether there were statistically significant differences between the means of three or more independent groups. The Chi-square test used for testing relationships between categorical variables. Spearman's RHO correlation was used to determine whether there was a significant relationship (i.e., correlation) between two variables. The results were evaluated within a 95% confidence limit, assuming $p < 0.05$ as the significance level.

Figure 2. Grade 1: Thymus with less than 50% fat content.

Results

The study reviewed a total of 465 patients (40.46±12.18 years), including 186 (40%) female (41.09±12.61), and 279 (60%) male patients (40.03±11.89 years).

Figure 1. Grade 0: Thymus in normal soft tissue density.

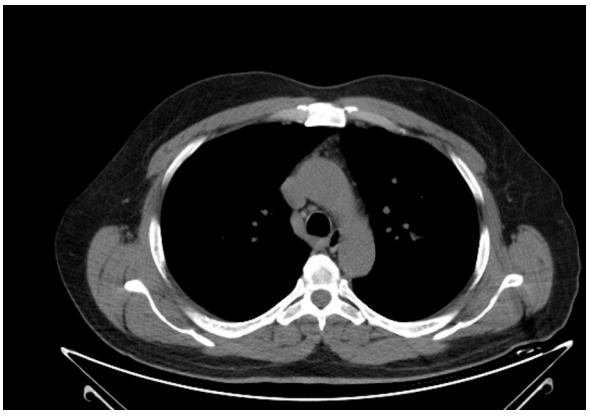

Figure 3. Grade 2: More than 50% greasiness.

Figure 4. Grade 3: Complete fatty degeneration.

Patients with CO-RADS categories 1 and 2 were considered negative for COVID-19 pneumonia, and categories 3, 4, and 5 were considered positive for COVID-19 pneumonia. The distribution of patients according to CO-RADS classification and pneumonia is given in Table I.

In this table, it is observed that the mean age increases as the CO-RADS category increases. For example, the average age of CO-RADS category one is 32.6 years, while the average age of category five is 46.0 years. In addition, the mean age of patients without pneumonia was 34.67 years, while the mean age of patients with pneumonia was 44.23 years.

The distribution of patients with COVID-19 pneumonia by age groups and gender are presented in Table II. It has been seen that the rate of having COVID-19 pneumonia increases as the age group increases.

Of the total, 260 (55.9%) patients were detected with thymus, including 104 (40%) female, and 156 (60%) male patients. The thymus gland was not detected in 205 (44.1%) patients, of which 82 were female. The distribution of thymus gland classification, according to age groups, is given in Table III. This table shows us that the thymus gland undergoes involution with age.

There was no statistically significant difference between the presence of thymus and the female-male gender using the Chi-Square test ($p = 1.000$). When the presence of thymus and age groups were compared using the ANOVA test, there was a statistically significant difference between the 20-29 age group and the 40-49 and 50-59 age group ($p < 0.001$).

In the patients with pneumonia, when the age groups were compared with the ANOVA test, there was a statistically significant difference between the 20-29 age group and the 40-49 and 50-59 age group ($p < 0.001$). No statistically significant difference between the presence of pneumonia and female-male gender was detected using the Chi-Square test ($p = 1.000$).

The distribution of COVID-19 pneumonia according to the thymus gland and thymus gland classification is presented in Table IV.

It was evaluated whether there was a statistical difference between the thymus gland groups (involution groups; thymus 0, 1, 2, 3) in terms of the presence of pneumonia. No statistically significant difference was observed between thymus 0 and thymus 1 ($p = 0.106$) and between thymus 2 and thymus 3 ($p = 1.000$) in terms of the presence of pneumonia. However, a statistically significant difference was observed between thymus

Table I. Distribution of patients according to CO-RADS classification and pneumonia.

	CO-RADS classification					
	1	2	3	4	5	Total
Female	49	25	21	39	52	186
Male	83	27	28	54	87	279
Total	132	52	49	93	139	465
Mean age and SD	32.6 ± 10.6	39.7 ± 13.3	40.9 ± 13.4	43.3 ± 1.1	46.0 ± 9.9	40.5 ± 12.2
	Pneumonia negative		Pneumonia positive			
Female	74		112			186
Male	110		169			279
Total	184		281			465
Mean age	34.67 ± 11.82		44.23 ± 10.86			40.5 ± 12.2

Data are presented as mean ± SD or N values. SD = Standard Deviation, N = number of patients.

Table II. Distribution of patients according to pneumonia, age groups, and gender.

Pneumonia	Gender	20-29 years		30-39 years		40-49 years		50-59 years		Total	
		Mean age	N	Mean age	N	Mean age	N	Mean age	N	Mean age	N
Yes	Male	24.79	24	35.07	26	44.47	63	55.00	56	43.72	169
	Female	24.56	16	36.37	16	44.97	35	55.40	45	45.02	112
	Total	24.70	40	35.57	42	44.65	98	55.17	101	44.23	281
No	Male	24.79	24	33.21	33	42.53	17	56.34	14	34.35	110
	Female	24.56	16	34.53	13	45.29	13	54.60	15	35.16	74
	Total	24.13	79	33.58	46	44.10	30	55.37	29	34.67	184

N: number of patients.

Table III. Distribution of thymus gland classification according to age groups.

Thymus classification	Age groups (patient's number)				Total
	20-29	30-39	40-49	50-59	
No thymus	20	20	77	88	205
Thymus 0	52	3	3	1	59
Thymus 1	34	35	10	0	79
Thymus 2	13	30	37	24	104
Thymus 3	0	0	1	17	18
Total	119	88	128	130	465

Table IV. Distribution of COVID-19 pneumonia by the thymus gland and thymus gland classification.

		Pneumonia			*p*
		No	Yes	Total	
Thymus	Yes	175 (37.6%)	85 (18.3%)	260 (55.9%)	< 0.001
	No	9 (1.9%)	196 (42.2%)	205 (44.1%)	
	Total	184 (39.6%)	281 (60.4%)	465 (100%)	
Thymus classification	0	53 (11.4%)	6 (1.3%)	59 (12.7%)	< 0.001
	1	62 (11.3%)	17 (3.7%)	79 (16.9%)	< 0.001
	2	51 (10.9%)	53 (11.4%)	104 (22.4%)	< 0.001
	3	9 (1.9%)	9 (1.9%)	18 (3.8%)	< 0.001

0 and thymus 2 ($p < 0.001$) between thymus 0 and thymus 3 ($p = 0.001$), between thymus 1 and thymus 2 ($p < 0.001$), and between thymus 1 and thymus 3 ($p = 0.020$) in terms of the presence of pneumonia.

The statistical relationship between the absence of the thymus gland and pneumonia by age groups is presented in Figure 5.

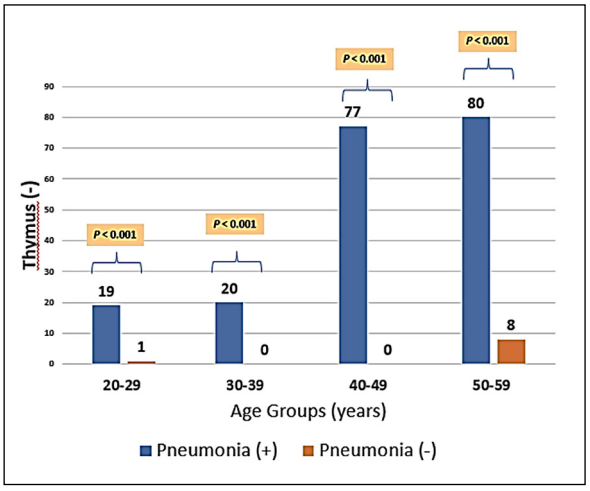

Figure 5. The statistical relationship between the absence of thymus gland and pneumonia by age groups.

The correlation between the presence of the thymus and pneumonia was investigated by Spearman's rho test. A negative correlation of -0.639 was found between the presence of the thymus and pneumonia. The fact that this result is between 0.5 and 0.74 shows us that there is a good degree of negative correlation.

When the presence of pneumonia and the presence of the thymus were compared using the Chi-Square test, a statistical difference ($p < 0.001$) was found. The number of infected lung segments and the distribution of the mean number of infected lung segments, according to the presence of the thymus, are presented in Table V. When the number of infected lung segments was evaluated, it was found that pneumonia was 3.85 times more common in patients without a thymus. On the other hand, when the mean number of infected lung segments was evaluated, it was found that the mean number of segments was 4.84 times higher in patients without a thymus.

Discussion

SARS-CoV-2 affects children less frequently than adults as MERS-CoV and SARS. In adults,

Table V. Distribution of infected lung segments and presence of thymus gland. Presence of thymus gland and distribution of the mean number of infected lung segments.

Lung segments			Thymus Yes	Thymus No	Rate of Thymus No/Yes	p*
Right	Superior lobe	Apical	28	32	1.14	0.128*
		Anterior	15	77	5.13	< 0.001*
		Posterior	38	136	3.57	< 0.001*
	Middle lobe	Lateral	22	136	6.18	< 0.001*
		Medial	28	145	5.1	< 0.001*
	Inferior lobe	Superior	52	143	2.75	< 0.001*
		Medial	24	166	6.91	< 0.001*
		Anterior	37	173	4.67	< 0.001*
		Lateral	55	184	3.34	< 0.001*
		Posterior	78	192	2.46	< 0.001*
Left	Superior Lobe	Apico-posterior	26	119	4.57	< 0.001*
		Anterior	11	60	5.45	< 0.001*
		Superior lingular	18	106	5.89	< 0.001*
		Inferior lingular	43	164	9.11	<0.001*
	Inferior Lobe	Superior	43	161	3.74	< 0.001*
		Anterior-basal	18	169	9.38	< 0.001*
		Lateral	45	184	4.09	< 0.001*
		Posterior	77	190	2.46	< 0.001*
Total number of infected lung segment			658	2,537	3.85	< 0.001*
The mean number of infected lung segments			2.53 ± 4.22	12.25 ± 4.77	4.84	< 0.001

*Fisher's Exact Test, **Chi-Square Test.

these infections are also common and more fatal[1]. Wang et al[6], Dhochak et al[7], and Hu et al[8] drew attention to an important point in their studies. It has been proven that SARS-CoV and MERS-CoV infections develop milder symptoms in children compared to adults[6-8]. Rehman et al[9] reported the mortality rate (percentage) among different age groups in COVID-19 in their study as follows. While there was no death in the 0-9 age range, this rate was found to be 0.2% in the 10-19 age range. However, it has been determined to be 1.3% in the 50-59 age range, 3.6% in the 60-69 age range, and 8% in the 70-79% age range[9].

An important cause of death from SARS-CoV-2 is pneumonia. In our study, we investigated the frequency of COVID-19 pneumonia in adult age groups. As shown in Table I, the incidence of pneumonia increases with age.

Chinese health authorities announced that two-thirds of the patients who died were male[10]. This raised an important question. Are males more susceptible to contracting and dying from COVID-19? Jin et al[11] found that males and females have the same prevalence, but males with COVID-19 are at risk of worse outcomes and death, regardless of age. In our study, pneumonia was detected in 281 (60.4%) of 465 patients. Of these patients with pneumonia, 112 (39.9%) were female and 169 (60.1%) were male. Similar to these data, the incidence of COVID-19 pneumonia was found to be higher in men than in women in our study.

While adults are more affected by the coronavirus disease 2019 (COVID-19) infection, children are less affected. It has been determined that patients with COVID-19 who have comorbidities such as cardiovascular disease, hypertension, chronic obstructive pulmonary diseases, obesity and diabetes have a higher risk of mortality[2]. It is a fact that COVID-19 mostly affects those with comorbidities. However, age is also an important risk factor in those without comorbidities. There is a direct correlation between age and COVID-19 severity and mortality[2]. Some researchers have suggested that this may be related to the loss of volume and function of the thymus gland with age[1-3].

The thymus is a largely neglected organ. However, it plays an important role in the regulation of adaptive immune responses[2]. The thymus is the main lymphoid organ that regulates the immune and endocrine systems by controlling thymic cell proliferation and differentiation. The gland is a primary lymphoid organ responsible for the generation of mature T cells into CD4+ or CD8+ single-positive T cells, and it contributes to cellular immunity. Regarding humoral immunity, thymic plasma cells secrete almost exclusively the two main complement-fixing effector IgG subclasses, IgG1 and IgG3[3]. The pathogenesis of a standard viral infection is as follows: the contact of the pathogen with the mucosa is initially followed by an innate immune response. The primary determinant of adaptive immunity is T cells. Regulatory T cells are active early in life and have an important role in immunomodulation. The thymus-mediated adaptive immune response is responsible for the immune response responsible for preventing the invasive damage of a virus. The thymus is very active in the intrauterine and neonatal periods; it begins to shrink after birth and it continues to be active until puberty. Loss of age-regulating T cell function causes difficulties in controlling the immune response and increased inflammation, as demonstrated as an inflammatory storm in coronavirus disease (COVID-19). Thymus and T cells are key factors in the pathogenesis of SARS-CoV-2 in children[1].

The decrease in the thymus gland volume and the accompanying gradual decrease in the number of T cells and their functions is called immunosenescence. With this condition, people become more susceptible to infections. It has also been revealed that regulatory T cell activity decreases with immunosenescence. This condition occurs as difficulty in controlling the immune response, increased inflammatory response, and an increased tendency to autoimmunity[1].

Clinical and pathological examination of coronavirus cases showed a cytokine storm associated with a dysregulated immune response. This caused extensive tissue damage. The main reason for this tissue damage was determined to be due to an out-of-control immune response caused by the virus[9]. The primary reason for the clinical picture in adult patients, especially in patients aged 50 and over, is the irregular, deficient and uncontrolled control caused by morphofunctional alterations (thymus involution) and immuno-aging. It has been suggested that there may be an undetectable antiviral response[1].

As far as we know, there are three publications about the relationship between the presence of the thymus gland and COVID-19 pneumonia[5,12,13]. Cuvelier et al[13] studied a total of 87 patients, 50 of whom had COVID-19 and 37 were controls. In the presence of the thymus in patients with COVID-19, a higher lung injury score was found, but a lower mortality rate (8.6% *vs.* 41.2%, $p < 0.001$). Other factors associated with mortality were age, lymphopenia, high CRP, and comorbidities. They suggested that the absence of thymus in elderly patients infected with SARS-CoV-2 may contribute to a worse prognosis[5,12,13]. Urfali et al[12] included a total of 66 patients, 33 of whom had COVID-19 pneumonia and 33 who did not have COVID-19. They examined thymus density ($p = 0.015$) and thymus/heart ratio ($p = 0.04$), and then reported that there was a significant difference between patients with COVID-19 infection and the control group[12]. Çakmak et al[5] included 87 COVID-19 patients in the study and reported a statistically significant relationship between increased thymus fat component and the presence of COVID-19 lung involvement ($r = 0.461$).

In our study, there was a statistical difference ($p < 0.001$) between the thymus gland groups (involution groups; thymus 0, 1, 2, 3) in terms of the presence of pneumonia (Table IV).

The relationship between the absence of the thymus gland and the presence of pneumonia was examined (Figure 1). Pneumonia was detected in 19 of 20 patients aged 20-29 years without a thymus gland. Pneumonia was detected in all patients aged 30-39 (20 patients) and 40-49 years old (77 patients without a thymus gland). Pneumonia was detected in 80 of 88 patients aged 50-59 years. There was a statistically significant difference between the absence of the thymus gland and the presence of pneumonia in all age groups ($p < 0.001$). This shows that there may be a relationship between the absence of the thymus gland and the presence of pneumonia.

Pneumonia was 3.85 times more common in patients without a thymus. On the other hand, the mean number of infected lung segments was 4.84 times higher in patients without a thymus. Correlation between the presence of thymus and pneumonia was investigated in this study. A negative correlation of -0.639 was found between the presence of the thymus and pneumonia. In short, the presence of the thymus is a good preventa-

tive for pneumonia. In this study, a statistically significant difference was found in terms of the presence of the thymus gland when the patients with and without COVID-19 pneumonia were compared.

Conclusions

For COVID-19 patients, there is a statistically significant correlation between the severity of lung findings on thorax CT examination and the level of involution in the patients' thymus tissue. The presence of the thymus may be a good preventative for pneumonia.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval
This retrospective study was conducted in accordance with the ethical principles of the declaration of Helsinki and approved by Malatya Turgut Ozal University Clinical Research Ethics Committee (08/03/2021, 2021/52).

Informed Consent
Informed consent was not required due to the retrospective nature of the study.

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Authors' Contribution
The study concept and design, data acquisition, data analysis and interpretation, and writing of manuscript were prepared by Bulent Petik.

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Data Availability
The data supporting this article are available from the corresponding author on reasonable request.

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