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Radiology

Epicardial adipose and pre-sternal subcutaneous tissues associated with extent of pneumonia and hospitalization in COVID-19

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ABSTRACT

Objectives: The aims of this study were, to analyze epicardial adipose tissue and pre-sternal adipose tissue thicknesses and the relationship of the ratio of these two parameters with radiological progression, age, gender, concomitant diseases, hospitalization, length of hospital stay, need for intensive care and survival status of COVID-19 patients.

Methods: In this retrospective study, a total number of 204 PCR-positive COVID-19 patients, who have initial lung computed tomography (CT) and a second CT within 15 days due to prolonged symptoms or suspected complications were included. According to patterns of lung involvement at the time of diagnosis, patients were divided into 4 groups. In initial CT scans, epicardial adipose tissue and pre-sternal subcutaneous adipose tissue thickness were measured. Progression or regression of the disease is evaluated by comparing the findings in initial and control CTs.

Results: The mean age, epicardial adipose tissue thickness (EAT), pre-sternal adipose tissue thickness (PAT), and the EAT/PAT ratio of patients with involvement in both lungs were found to be higher than those in patients with one lung or without lung involvement and there was a statistically significant positive correlation between them.

Conclusions: This study is thought to be the first in which epicardial adipose tissue and pre-sternal adipose tissue were evaluated together in COVID-19 patients. Epicardial adipose tissue is a metabolically active organ and measurement in initial CT scans may give an easy and quick idea of the evolution of the disease.

Keywords: COVID-19, epicardial adipose tissue, lung inflammation, disease evolution

COVID-19 has emerged as a multisystem complex infectious disease that predominantly affects the lungs and has become a global health problem since it was first identified in December 2019. It is of vital importance to learn about the effects of this pandemic, which continues to threaten human health worldwide. However, it is clear that defining and understanding the different pathogeneses and pathways that explain the severity of clinical findings can facilitate the creation of possible treatment alternatives and the management of patients' clinical findings [1].

Although most patients survive the disease without

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symptoms or with mild symptoms, the disease results in hospitalization with severe symptoms in approximately 20% of cases, with 58% of patients requiring intensive care. Acute respiratory complications may require hospitalization in the intensive care unit for an extended period, and this is one of the major causes of mortality and morbidity in patients [2].

Computed tomography of the thorax is a highly sensitive method in the diagnosis of COVID19 pneumonia and in defining the severity of lung involvement [3]. Epicardial adipose tissue is an active endocrine organ that modulates the metabolic environment of both the coronary arteries and myocardium [4]. Various studies have shown that EAT volume measured by CT is associated with lung function in both healthy individuals and patients with chronic lung disease [5, 6]. Furthermore, the relationship between CT-derived EAT measurement and circulating inflammatory markers, and cardiometabolic risk factors has also been demonstrated [7, 8]. There are assumptions that COVID-19 triggers an immune-mediated systemic inflammatory response and that this inflammation affects the heart via EAT [9, 10]. Besides, EAT volume can potentially accelerate ectopic intrapulmonary fat reserves and increase local lung infiltration [11, 12].

In the light of this information, the present study aims to analyze epicardial adipose tissue and pre-sternal adipose tissue thickness and the relationship of the ratio of these two parameters to each other with radiological progression, age, gender, concomitant diseases, length of hospital stay, need for intensive care unit and survival status of patients.

METHODS

This retrospectively designed study examined initial lung CTs of patients with PCR-positive COVID19 infection. Patients, who had a second CT within 15 days due to prolonged symptoms or suspected complications were included in the study. Patients younger than 18 years of age, with a diagnosis of malignancy, underwent thoracic surgery, and those presented with accompanying pleural effusion or trauma were excluded from the study.

The patients' age, gender, co-morbidities, length of hospitalization, need for intensive care unit, and survival status was researched. A total of 204 patients were included in the study. According to the lung involvement pattern in the initial CT, 4 groups were formed; patients with pneumonia in both lungs (Group 1), patients with pneumonia in one lung but more than one area (Group 2), patients with one focal lung infiltration (Group 3) and patients with normal lung findings (Group 4).

CT imaging of all patients was performed with Philips Ingenuity 128 multi-slice CT device. At the time of diagnosis, epicardial adipose tissue thickness was measured at the level in the front of the right atrium, where it was the widest and pre-sternal subcutaneous adipose tissue thickness was measured from the mid-xiphoid bone level. Progression or regression evaluation was performed by comparing the findings in the second CTs. The relationship between epicardial adipose tissue thickness, pre-sternal fat tissue thickness, and the ratio of these two to radiological progression, the duration of hospitalization, the need for intensive care and length of stay, and survival status were evaluated.

All procedures were performed by institutional ethics committee approval and the Declaration of Helsinki. Approval, numbered 2017-KAEK-120 /2/2021.K-21, was obtained from the Ethics Committee of İstinye University.

Statistical Analysis

The SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk Francia test, while the homogeneity of variance was evaluated with the Levene test. The Kruskal-Wallis H test was used according to the Monte Carlo simulation results to compare more than two groups with each other according to the quantitative data, while 's test was used for Post Hoc analysis. The Spearman's rho tests were used to examine the correlations of the variables with each other. In the comparison of categorical variables, the Pearson Chi-Square and Fisher-Freeman-Holton tests were tested with the Monte Carlo Simulation technique, and the column ratios were compared with each other and expressed according to the Benjamini-Hochberg corrected *p* - value results. While quantitative variables were expressed as mean (standard deviation), Median (Minimum / Maximum), and Median (Percentile 25 / Percentile 75) in the tables, categorical variables were shown as n (%). The variables were analyzed at the 95% confidence level and were considered significant when the p - value was less than 0.05.

RESULTS

The mean age of 204 patients was 45.62 ± 16.28 years and 130 (65%) were male. There was no statistically significant difference between the groups in terms of gender (p = 0.119). The mean epicardial fat thickness was 18.89 ± 13.76 mm, and the mean pre-sternal fat tissue thickness was 11.75 ± 5.66 mm, and the EAT/PAT ratio was 1.82 ± 1.5 in the whole study group. All the patients were researched for concomitant diseases. The frequency of diabetes mellitus and bronchial asthma was found to be statistically significantly higher in patients with involvement of both lungs (Group 1), compared to other groups (p = 0.023 and p = 0.032, respectively). There was no significant difference between the groups in terms of the frequencies of hypertension, coronary artery disease, and chronic obstructive pulmonary disease (p > 0.05). The comorbidities, CT findings, and clinical features associated with COVID-19 are summarized in Table 1. The mean age, epicardial adipose tissue thickness, pre-sternal adipose tissue thickness, EAT/PAT ratio, length of stay in the department and intensive care unit, and the mortality rates of the patients in Group 1 (both lung involvement) were found to be statistically significantly higher than those in the other groups (p < 0.05) (Table 2). The mean age of the patients in Group 1 was significantly higher than that of the patients in the other groups (p < 0.001). The EAT thickness of the

Table 1. Distribution analysis of patients

	n	%
Gender (Male)	130	65.0
Control CT results		
Progressed	81	40.5%
Regressed	95	47.5
Stable	24	12.0
Ex patients	9	4.5
Hospitalized patients	86	43,0
Patients with intensive care hospitalization	15	7.7
Hypertension	39	20.3
Coronary artery disease	13	6.8
Diabetes mellitus	20	10.5
Chronic obstructive pulmonary disease	12	6.3
Chronic renal railure	3	1.6
Asthma bronchial	14	7.3
	Mean ± SD	**Median (min-max)**
Age (years)	45.62 ± 16.28	44 (17-87)
Epicardial adipose tissue measurement (mm)	18.89 ± 13.76	15 (1-75)
Pre-sternal adipose tissue measurement (mm)	11.75 ± 5.66	10 (3-36)
EAT/PAT	1.82 ± 1.50	1.33 (0.11-7.92)
Length of stay in the department (days)	5.05 ± 7.64	0 (0-52)
Length of stay in the ICU (days)	1.24 ± 5.98	0 (0-52)

SD = Standard Deviation

Table 2. **Comparison of clinical features and demographic data of patients according to their lung involvements**

	Group 1 (n = 85)	Group 2 (n = 71)	Group 3 (n = 25)	Group 4 (n = 19)	*p* value
Age, median (q1/q3)	51 (17/87) [bcd]	42 (19/86) [d]	39 (21/83) [d]	26 (21/51)	**< 0.001[k]**
Gender, n (%)					
Female	24 (28.2)	29 (40.8)	7 (28.0)	10 (52.6)	0.119 [c]
Male	61 (71.8)	42 (59.2)	18 (72.0)	9 (47.4)	
Epicardial adipose tissue measurement (mm), median (q1/q3)	28 (3.5/75)[bcd]	12 (3/32)	10 (2/30)	8 (1/22)	**< 0.001[k]**
Presternal adipose tissue measurement (mm)	12 (3.3/30)[bcd]	10 (3/36)	8 (4/22)	10 (7/25)	**< 0.001[k]**
EAT/Presternal ratio	2 (0.23/7.92)[bcd]	1.15 (0.23/7.62)[d]	1.17 (0.33/3)[d]	0.8 (0.11/3.14)	**< 0.001[k]**
Length of stay in the department (days)	8 (0/52) [bc]	1 (0/20)	2 (0/22)	5 (0 / 15)	**< 0.001[k]**
Length of stay in the ICU (days)	0.5 (0/52) [d]	0.5 (0 / 37)	0.5 (0 / 12)	0 (0 / 0)	**0.012[k]**
Mortality, n (%)					
Survived	78 (91.8)	71 (100.0) [ac]	23 (92.0)	19 (100.0)	**0.028[f]**
Ex	7 (8.2) [b]	0 (0.0)	2 (8.0) [b]	0 (0.0)	
Stay in the department, n (%)					
Absent	28 (32.9)	56 (78.9) [a]	20 (80.0) [a]	10 (52.6)	**< 0.001[c]**
Present	57 (67.1) [bc]	15 (21.1)	5 (20.0)	9 (47.4)	
Stay in the ICU, n (%)					
Absent	69 (85.2)	70 (98.6) [a]	23 (92.0)	19 (100.0)	**0.008[f]**
Present	12 (14.8) [b]	1 (1.4)	2 (8.0)	0 (0.0)	
Hypertension, n (%)					
Absent	64 (77.1)	50 (76.9)	21 (84.0)	18 (94.7)	0.319[f]
Present	19 (22.9)	15 (23.1)	4 (16.0)	1 (5.3)	
Coronary artery disease, n (%)					
Absent	76 (91.6)	61 (93.8)	23 (92.0)	19 (100.0)	0.695[f]
Present	7 (8.4)	4 (6.2)	2 (8.0)	0 (0.0)	
Diabetes mellitus, n (%)					
Absent	67 (81.7)	61 (95.3) [a]	23 (92.0)	19 (100.0) [a]	**0.023[f]**
Present	15 (18.3) [bd]	3 (4.7)	2 (8.0)	0 (0.0)	
Chronic obstructive pulmonary disease, n (%)					
Absent	74 (90.2)	61 (93.8)	25 (100.0)	19 (100.0)	0.284[f]
Present	8 (9.8)	4 (6.2)	0 (0.0)	0 (0.0)	
Chronic renal railure, n (%)					
Absent	82 (98.8)	64 (98.5)	24 (96.0)	19 (100.0)	0.657 [f]
Present	1 (1.2)	1 (1.5)	1 (4.0)	0 (0.0)	
Bronchial asthma (n/%)					
Absent	80 (96.4)	57 (87.7)	25 (100.0)	16 (84.2)	**0.032[f]**
Present	3 (3.6)	8 (12.3)	0 (0.0)	3 (15.8)	

[k]Kruskal-Wallis Test (Monte Carlo), Post Hoc Test = Dun's Test, [c]Pearson Chi-Square Test (Monte Carlo), [f]Fisher Freeman Halton Test (Monte Carlo), Post Hoc Test, Benjamini Hochberg Multiple Testing Correction, q1= 1[st] quartile, q3 = 3[rd] quartile $p < 0.05$ considered as significant.

patients in Group 1 was found to be significantly higher than in other groups ($p < 0.001$). Also, the pre-sternal fat thickness was found to be significantly higher in Group 1 patients compared to that in Group 2 and Group 3 patients ($p = 0.004$ and $p < 0.001$, respectively). There was no significant difference between Group 1 and Group 4 in this respect ($p > 0.05$). In the comparison of Group 2, 3 and Group 4 patients to each other in terms of epicardial adipose tissue thickness, EAT/PAT ratio, and pre-sternal adipose tissue thickness, no statistically significant difference was found ($p > 0.05$).

Table 3. Correlation findings of EAT, epicardial adipose tissue thickness, and EAT/PAT ratio of the groups

	Age		Length of stay in the department (days)		Length of stay in the ICU (days)		Follow-up period	
	r	*p*	r	*p*	r	*p*	r	*p*
Group 1								
Epicardial adipose tissue measurement (mm)	0.251	**0.021**	0.074	0.500	-0.048	0.673	0.071	0.531
Presternal adipose tissue measurement (mm)	0.045	0.684	0.216	**0.047**	-0.015	0.893	0.190	0.089
EAT/PAT	0.266	**0.014**	-0.085	0.441	-0.001	0.990	-0.054	0.631
Group 2								
Epicardial adipose tissue measurement (mm)	0.460	**< 0.001**	0.053	0.663	0.162	0.185	0.070	0.568
Presternal adipose tissue measurement (mm)	0.214	0.077	0.184	0.131	-0.027	0.823	0.178	0.144
EAT/PAT	0.200	0.099	-0.084	0.490	0.149	0.221	-0.067	0.584
Group 3								
Epicardial adipose tissue measurement (mm)	0.243	0.242	-0.227	0.276	-0.064	0.761	-0.259	0.212
Presternal adipose tissue measurement (mm)	0.180	0.390	-0.161	0.442	-0.016	0.938	-0.137	0.512
EAT/PAT	0.210	0.314	-0.214	0.303	0.025	0.907	-0.211	0.312
Group 4								
Epicardial adipose tissue measurement (mm)	0.128	0.603	0.045	0.854	-	-	0.045	0.854
Presternal adipose tissue measurement (mm)	0.386	0.102	0.123	0.615	-	-	0.123	0.615
EAT/PAT	-0.121	0.622	0.108	0.658	-	-	0.108	0.658
Total								
Epicardial adipose tissue measurement (mm)	0.518	**< 0.001**	0.250	**< 0.001**	0.117	0.103	0.270	**< 0.001**
Presternal adipose tissue measurement (mm)	0.219	**0.002**	0.230	**0.001**	0.024	0.743	0.219	**0.002**
EAT/PAT	0.407	**< 0.001**	0.105	0.142	0.146	0.043	0.138	0.055

Spearman's Rhotest, r: Correlation Coefficient $p < 0.05$consideredtobesignificant

While a significant positive correlation was found between epicardial adipose tissue thicknesses and age, length of hospital stays, and follow-up periods in all patient groups (r = 0.518, $p < 0.001$; r = 0.250, $p < 0.001$; and r = 0.270 $p < 0.001$, respectively), no correlation was found between the length of intensive care stays (r = 0.117, $p = 0.103$). Again, there was a significant positive correlation between pre-sternal adipose tissue thickness and age, length of hospital stays, and follow-up periods of the patients (r = 0.219, $p = 0.002$; r = 0.230, $p = 0.001$; and r = 0.219 $p = 0.002$, respectively), but no correlation was found between the pre-sternal adipose tissue thickness and the duration of intensive care unit (r = 0.024, $p = 0.743$). All groups showed a significant positive correlation between the EAT/PAT ratio and age (r = 0.407, $p < 0.001$). A significant positive correlation was found between epicardial fat thickness, EAT/PAT ratio, and age in patients with involvement in both lungs (r = 0.251 $p = 0.021$, r = 0.266 $p = 0.014$). There was a significant positive correlation between epicardial adipose tissue thickness and ward length of stay in patients with involvement in both lungs (r = 0.216, $p = 0.047$). There was also a significant positive correlation between epicardial fat measurement and age in patients with involvement in one-lung (r = 0.460. $p < 0.001$) (Table 3).

In the comparison made according to the progression of the control CT findings of the patients in Group 1 and Group 2, it was found that there was no difference between EAT thickness, and the EAT/PAT ratio of the patients with and without progression ($p > 0.05$). However, in the evaluation of all patients, EAT thickness and the EAT/PAT ratio of patients with progressive CT findings were found to be statistically significantly lower ($p < 0.001$ and $p < 0.001$, respectively).

DISCUSSION

The current study determined that there was a statistically significant positive correlation between epicardial adipose tissue thickness, pre-sternal adipose tissue thickness, EAT/PAT ratio, age, and the length of hospital stays of patients diagnosed with COVID-19. The mean age, EAT thickness, pre-sternal adipose tissue thickness, and the EAT/PAT ratio of patients with involvement in both lungs were found to be significantly higher than those in patients with involvement in one lung or without lung involvement.

A high BMI (> 28 kg/m2) and diabetes mellitus were defined as two different independent risk factors that were also associated with the severity of COVID-19 disease. According to the reports of the Center for Disease Control and Prevention of the People's Republic of China, cardiovascular diseases, chronic respiratory diseases, hypertension, diabetes mellitus and cancer increase the risk of death in patients diagnosed with COVID-19 [13]. These diseases mentioned in the published report occur as a result of chronic immune activation in the adipose tissue, liver, pancreas, and vascular system [14]. The contribution of obesity to the increase in inflammatory markers as a result of immune activation is very important. The relationship between hypertension, cardiovascular disease, diabetes mellitus, respiratory disease pathogenesis, and obesity also supports this statement [15, 16]. In this study, the frequency of diabetes mellitus and asthma bronchial was found to be statistically significantly higher in patients with involvement of both lungs compared to that of other groups.

In previous studies, abdominal visceral adipose tissue measured by CT is associated with critical illness in COVID-19 patients [17], but there is not sufficient data on thoracic fat stores. EAT measurements using CT are strongly associated with abdominal visceral adiposity and metabolic risk factors and coronary atherosclerosis [18, 19]. Considering the high spatial resolution of CT and the discrete attenuation values of adipose tissue, EAT volume and density can be measured easily and precisely [20]. Structural and functional properties of visceral and subcutaneous adipose tissue differ from each other. There are molecular, physiological, clinical, and prognostic differences between subcutaneous and visceral adipose tissue in addition to the anatomical region and cellular structure. The visceral adipose tissue found in the mesentery and omentum has more cellular, vascular, and neural innervation structure compared to the subcutaneous adipose tissue and contains more inflammatory and immune cells, less preadipocyte differentiation capacity, and a large number of large adipocytes [21]. It is thought that the imbalance between anti- and pro-inflammatory adipokine secretion from EAT may play a role in the formation of the cytokine storm in critically ill COVID-19 patients. The relationship between EAT thickness and lung involvement in patients diagnosed with COVID19 disease in the current study may be important.

Different results have been shared in a few publications in the literature evaluating the relationship between EAT thickness and COVID-19 disease findings. In the study by Grodecki *et al*. [21], EAT thickness and EAT attenuation were reported to be associated with clinical worsening and mortality. Deng *et al*. [22], reported that EAT attenuation was lower in patients with severe COVID-19 compared to patients with mild disease, and EAT volume was found to be significantly higher in patients with severe COVID-19 disease. However, in a retrospectively designed study by Iacobellis *et al*. [23], non-gated CT scans of mild and severe COVID-19 patients were evaluated, and EAT thickness was not significantly different among patients with different severities of COVID-19, but EAT attenuation increased significantly with the increase in the severity of COVID-19 [24]. In the current study, epicardial adipose tissue and pre-sternal fat thickness were found to be antly higher in patients with involvement in both lungs.

While the disease primarily affects the respiratory tract, it can lead to multi-organ failure and can be fatal. Acute respiratory complications may require hospitalization in the intensive care unit for a long time and constitute one of the major causes of mortality and morbidity in these patients [25].

Patients admitted to the intensive care unit are generally older and have multiple morbidities, including hypertension and diabetes. Factors associated with increased mortality are advanced age, comorbid diseases (hypertension, diabetes, cardiovascular diseases, chronic lung diseases, and cancer), high disease severity score, high D-dimer, high C-reactive protein levels, and high serum ferritin levels, lymphopenia, and secondary infections [26].

This study is thought to be the first study in which epicardial adipose tissue and pre-sternal adipose tissue were evaluated together in patients diagnosed with COVID-19. A significant positive correlation was found between epicardial fat thickness and EAT/PAT ratio and age in patients with involvement of both lungs. Again, a significant positive correlation was found between epicardial adipose tissue thickness and service length of stay in patients with involvement of both lungs.

Limitations

While the retrospective design of our study, the presence of a relatively low number of patients, and the absence of body mass index data can be counted as shortcomings of the study, the combined evaluation of EAT and subcutaneous adipose tissue in patients with a diagnosis of COVID-19 can be considered strengths.

CONCLUSION

In conclusion, our current knowledge indicates that inflammation plays an important role in the development and progression of COVID-19 disease. The epicardial adipose tissue which is a metabolically active organ is accepted as a new marker of inflammation, it can be easily analyzed on CT scans. Especially in patients with both lung involvement, we can say that morbidity and mortality of COVID-19 patients increase with increasing EAT/PAT ratio.

Authors' Contribution

Study Conception: FST, ŞYT; Study Design: FST, ŞYT; Supervision: FST, ŞYT; Funding: N/A; Materials: N/A; Data Collection and/or Processing: FST, ŞYT GK; Statistical Analysis and/or Data Interpretation: FST; Literature Review: FST, ŞYT; Manuscript Preparation: FST and Critical Review: FST, ŞYT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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