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Comparison of Thorax Computed Tomography Based Body Composition Parameters Between COVID-19 Positive and Negative Patients: A Cross-Sectional Study

COVID-19 Pozitif ve Negatif Hastalar Arasında Toraks Bilgisayarlı Tomografi Tabanlı Vücut Kompozisyon Parametrelerinin Karşılaştırılması: Kesitsel Bir Çalışma

Duygu İMRE YETKİN[a], Yeliz ÇİÇEK[b], Hıdır SARI[c], Cihan AKGÜL ÖZMEN[d]

[a]Clinic of Radiology, Midyat State Hospital, Mardin, Türkiye
[b]Department of Clinical Microbiology and Infectious Diseases, Dicle University Faculty of Medicine, Diyarbakır, Türkiye
[c]Department of Public Health, Dicle University Faculty of Medicine, Diyarbakır, Türkiye
[d]Department of Radiology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

ABSTRACT Objective: To compare body fat-muscle and visceral obesity indices that can be measured with thorax computed tomography (CT) between reverse transcriptase-polymerase chain reaction (RT-PCR) positive and negative patients. **Material and Methods:** This retrospective, comparative study included 141 PCR (+) and 150 PCR (-) patients who applied to our hospital with flu-like symptoms without having the comorbid diseases and undergone thoracic CT between April 1, 2020-July 1, 2020. For the each patient, the ratio of thoracic subcutaneous adipose tissue thickness to pectoralis major muscle thickness (TSAT/PMJ), epicardial adipose tissue thickness (EAT), liver density (LD), abdominal subcutaneous adipose tissue thickness to psoas major muscle thickness ratio (ASAT/ PSM), subcutaneous abdominal adipose tissue thickness to erector spinae muscle thickness ratio (ASAT/ESM) was measured. The comparison was made between the subgroups in terms of age, gender, and measured parameters. **Results:** Statistically significant difference was found between PCR (+) and (-) individuals in terms of EAT mean ($p<0.05$). TSAT/PMJ, ASAT/PSM and ASAT/ESM ratios were higher in women ($p <0.05$). The mean EAT in men was increased in the PCR (+) group ($p<0.05$). In PCR (+) group, LD decreased, EAT increased with increasing age ($p<0.05$). PCR (+) and PCR (-) groups didn't show significant difference ($p>0.05$) in terms of TSAT/PMJ, ASAT/PSM, LD, ASAT/ESM. **Conclusion:** Higher EAT values can increase the risk of getting coronavirus disease-2019 (COVID-19) infection. Peripheral fat-muscle indices don't increase the risk of contracting COVID-19 infection.

Keywords: COVID-19 infection; obesity; thorax computed tomography

ÖZET Amaç: Ters transkriptaz-polimeraz zincir reaksiyonu [polymerase chain reaction (RT-PCR)] pozitif ve negatif hastalarda toraks bilgisayarlı tomografi (BT) ile ölçülebilen vücut yağ-kas ve viseral obezite indekslerini karşılaştırmaktır. **Gereç ve Yöntemler:** Bu retrospektif, karşılaştırmalı çalışmaya, 1 Nisan 2020-1 Temmuz 2020 tarihleri arasında hastanemize, grip benzeri semptomlarla yandaş hastalıkları olmaksızın başvuran ve toraks BT'si bulunan, 141 PCR (+) ve 150 PCR (-) hasta dâhil edildi. Her hasta için torasik subkütan yağ dokusu kalınlığının pektoralis majör kası kalınlığına oranı [thoracic subcutaneous adipose tissue/major muscle thickness (TSAT/PMJ)], epikardiyal yağ dokusu kalınlığı [epicardial adipose tissue thickness (EAT)], karaciğer yoğunluğu [liver density (LD)], abdominal subkütan yağ dokusu kalınlığının psoas majör kası kalınlığına oranı [abdominal subcutaneous adipose tissue thickness/psoas major muscle thickness (ASAT/PSM)], subkütan karın yağ dokusu kalınlığının erector spinae kası kalınlığına oranı [erector spinae muscle (ASAT/ESM)] ölçüldü. Alt gruplar arasında yaş, cinsiyet ve ölçülen parametreler açısından karşılaştırma yapıldı. **Bulgular:** PCR (+) ve (-) bireyler arasında EAT ortalamaları açısından istatistiksel olarak anlamlı fark bulundu ($p<0,05$). TSAT/PMJ, ASAT/PSM ve ASAT/ESM oranları kadınlarda daha yüksekti ($p<0,05$). Erkeklerde ortalama EAT PCR (+) grubunda arttı ($p<0,05$). PCR (+) grubunda yaş arttıkça LD azaldı, EAT arttı ($p<0,05$). PCR (+) ve PCR (-) grupları TSAT/PMJ, ASAT/PSM, LD, ASAT/ESM açısından anlamlı farklılık göstermedi ($p>0,05$). **Sonuç:** Yüksek EAT değerleri, koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] enfeksiyonuna yakalanma riskini artırabilir. Periferik yağ-kas indeksleri, COVID 19 enfeksiyonu olan ve olmayan hastalarda farklılık göstermemektedir.

Anahtar Kelimeler: COVID-19 enfeksiyonu; obezite; toraks bilgisayarlı tomografisi

Correspondence: Duygu İMRE YETKİN
Clinic of Radiology, Midyat State Hospital, Mardin, Türkiye
E-mail: duyguimre0831@gmail.com

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Coronavirus disease-2019 (COVID-19) is a droplet-mediated human to human transmitted virus caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).[1] World Health Organization declared SARS-CoV-2 as a pandemic agent on March 11, 2020. It has affected approximately 166 million people, 3.4 million people died by May 22, 2021. This virus may cause symptoms in patients such as fever, fatigue, myalgia and pneumonia etc.[2] Coronary artery disease (CAD), older age, diabetes mellitus (DM), hypertension (HT) and obesity increase the risk of SARS-CoV-2-related morbidity and mortality.[3] Severe obesity [body mass index (BMI)≥40 kg/m^2] was reported an important high-risk condition for COVID-19.[4] Obesity is an independent risk factor for hospitalization, severe disease, and death in patients with COVID-19.[5] Obesity is considered to create an exaggerated chronic inflammation with an increased circulating- levels of pro-inflammatory proteins, and it occurs not only in adults but also in adolescents and children.[6] In the severe COVID-19 infection, excessive inflammatory host response to SARS-COV-2 leads to high levels of circulating cytokines and this cytokine storm may result in death.[7,8]

Body composition can affect the clinical outcome of patients with pneumonia.[9,10] Buchman et al. revealed an independent relationship between respiratory and extremity muscle strength and mortality from pneumonia.[11]

Epicardial fat thickness or volume and liver density are measurable components of visceral obesity with unenhanced thorax computed tomography (CT). Epicardial adipose tissue thickness (EAT) is a visceral adipose tissue located between myocardium and visceral pericardium, and reported as an important indicator of visceral obesity and high cardiovascular risk independent of BMI.[12] Hepatic steatosis is closely associated with visceral obesity and excessive BMI.[13]

Based on aforementioned data, our main objective is to compare PCR positive and negative patients in terms of thoracic subcutaneous adipose tissue/major muscle thickness (TSAT/PMJ), EAT, liver density (LD), abdominal subcutaneous adipose tissue thickness/psoas major muscle thickness (ASAT/PSM) and ASAT/erector spinae muscle (ESM), thus to show the correlations of these parameters with getting COVID-19 infection.

MATERIAL AND METHODS

PATIENT SELECTION

This is a retrospective study conducted at our radiology department from June 1, 2021-June 25, 2021. We got the ethics committee approval from the Dicle University Faculty of Medicine (date: 30 June, 2021, no: 336). Approval for the study was also obtained from the Turkish Ministry of Health. Informed consent was waived due to the retrospective nature of the study. This study was conducted in accordance with the principles of the Helsinki Declaration.

We included 341 consecutive patients admitted to our hospital between April 1 2020-July 1 2020, and who had both chest CT and reverse transcriptase (RT)-PCR. Patients with thorax CT scan taken just before or within 24 hours after the PCR sample was taken were identified by an infectious disease resident with 4 years of experience. Age and gender of the patients were recorded from the hospital database. Patients with DM, HT and CAD were excluded as it may affect the measurements. In addition, patients with diseases affecting muscle thickness such as chronic obstructive pulmonary disease and malignancy were also excluded from the study. PCR (-) patients who applied to the hospital again with similar complaints were excluded from the study to eliminate false negativity. Patients under the age of 18, CT of patients with motion, respiratory and pulsation artifact that would prevent the measurement of EAT, patients with significant ventral diastasis, patients with cardiac pacemaker were excluded from the study because they may cause errors in the measurement of the indices. Patients with massive pericardial effusion, and polycystic liver disease were also excluded. Fifty patients were excluded for the reasons mentioned above. Remaining 291, 141 PCR positive and 150 PCR negative, ≥18-year-old patients were included to our study.

COLLECTION AND EVALUATION OF SWAB SAMPLES

Swab samples of patients with clinically suspicious for COVID-19 were obtained by avoiding touching the tongue, teeth and gums, and using a thin-handled sterile swap (dacron/polyester swap) in the form of a combined oropharyngeal and nasopharyngeal swab. The samples were taken and delivered to the microbiology laboratory with cold chain as recommended by the Ministry of Health guidelines. For each sample, 200 µL of clinical sample in transport medium was studied in biological safety by adding 200 µL of Bacterial Lysis Buffer (Roche). The nucleic acid extracts were frozen once prior to testing with the TIB MOLBIOL/Roche z 480 Assay. When the reaction was completed, the amplification curves from the fluorescent reading channels were examined and non-sigmoidal curves were recorded as negative. The result was recorded as positive if the curve was sigmoidal quantification cycle (Cq) ≤ 36 for the HEX channel and Cq ≤38 for the other channels.

CT ACQUISITION PARAMETERS AND EVALUATION

All CT examinations were performed in a Somatom Emotion 16-slice (Siemens Healthcare, Muenchen, Germany) with 1 mm slice thickness, in supine position, without contrast agent, with breath-holding, from thoracic inlet to the mid-portion of the kidneys. We used the first CT scan of the patients at the time of diagnosis. Technical parameters for CT scans were: tube voltage:90-120 kilovolt, mAS (milliampere-per second) was calculated with otomatic exposure control system (CARE Dose 4D), pitch:0.8, gantry rotation time:0.6 second, collimation:1.2 mm, window width:400 HU, window level:40 HU, FOV:364 mm, Kernel: B30S medium smooth.All images were obtained from picture archiving communication systems (PACS). All images were evaluated at the workstation (Siemens Healthcare, Germany), by a 7-year and 25-year experienced radiologists by consensus, unaware of PCR results.

MEASUREMENT OF VISCERAL AND PERIPHERAL OBESITY INDICES

PMJ thickness was calculated at the level of just above the aortic arch because it was found to give better results, in a single axial slice, at the midline, anteroposterior diameter (A-P) of the muscle, on the right and left.[14] TSAT measurement obtained for each side at the same level and location as PMJ thickness measured. A-P thickness of TSAT obtained from the PMJ's anterior border to dermis (Figure 1A). The final TSAT/PMJ ratio was found by taking the average of the two sides.

EAT mean was measured from the myocardial wall to the pericardium, by taking the average of right atrioventricular groove, left atrioventricular groove and interventricular groove values.[15] Measurements were taken from one-slice, 4 chamber horizontal mediastinal view (Figure 1B).

ASAT was measured at the level of L1-L2 vertebrae (lowest level of the thorax CT sections in our institute), 5 cm lateral to the linea alba as stated previously, on the right and left separately, in a single axial section.[16] PSM thickness was measured the middle part of the muscle at the L1-2 level (Figure 1C).

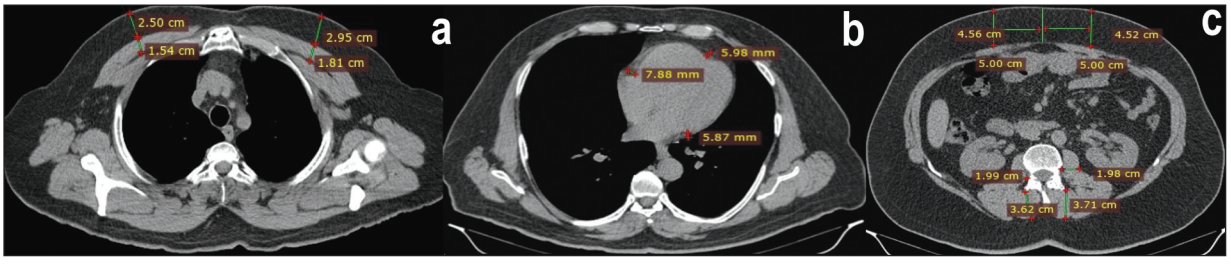

FIGURE 1: Unenhanced thorax CT in the mediastinal window of a 51-year-old male PCR (-) patient, **A)** Level of just above the aortic arc, TSAT/PMJ ratio, **B)** Four chamber horizontal view, right, left and interventricular groove EAT, **C)** At L1-L2 level, ASAT/PSM, and ASAT/ESM measurements are shown.
CT: Computed tomography; PCR: Polymerase chain reaction; TSAT/PJM: Thoracic subcutaneous adipose tissue/major muscle thickness; EAT: Epicardial adipose tissue thickness; ASAT/PSM: Abdominal subcutaneous adipose tissue thickness/psoas major muscle thickness; ESM: Erector spinae muscle.

L3 level was reported as the best point for this measurement, this level was not present in thorax CT sections. ASAT/PSM ratio was found for each side.[17] The results were recorded by averaging the ratios.

ASAT/ESM ratios were calculated at the same level as ASAT/PSM. ESM thickness was measured from the vertebral transverse process to the posterior border of ESM. ASAT was measured same as above described, ASAT/ESM ratios were calculated for each side and mean of the ratios were enrolled (Figure 1C).

An attenuation value of ≤40 Hounsfield units (HU), measured in the region of interest (ROI), in the unenhanced phase, have a correlation with a pathological fat content of ≥30% means moderate hepatic steatosis.[18] Previously data was stating that liver fat is homogeneous and measuring from a single section is sufficient, measurements were made from 3 different segments in order not to miss the effect of inhomogeneous fatty areas.[19] LD was measured for each 10 cm^2 -area from three axial view, segments 2-3, 5-8 and 6-7 with a freehand ROI, vascular structures, biliary tree and cystic-solid lesions were spared from the ROI space (Figure 2A, Figure 2B, Figure 2C). The average density of these three segments was recorded.

The above-mentioned measurements were repeated 3 times and the results were recorded by taking the average of these measurements.

STATISTICAL ANALYSIS

IBM SPSS Statistics 25 Macosx Version: 25.0.0.0 (Armonk, New York) statistical package program was used for the analysis of the data. Group means of continuous measurements were shown as ($\bar{X}$)±standard deviation (SD). Since the parametric assumptions were not realized, the non-parametric Mann-Whitney U test was used to compare the two averages. Correlation between CT measurement results and age variable was made using Spearman's correlation analysis since parametric assumptions were not met. It was evaluated by Spearman's correlation analysis coefficient (rs). In the analysis, Spearman's correlation coefficient (rs) results were 0.00-0.24 (weak), 0.25-0.49 (moderate), 0.50-0.74 (strong) and 0.75-1.00 (very strong); sign (-) was evaluated as negative correlation and positive (+) as positive correlation. As a result of all analyzes, $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the participants in the study was 47.9±19.3 years, 43.99% (n=128) were female and 56.01% (n=163) were male. The mean age of women was 47.1±18.8 (18-95), men was 48.6±19.6 (18-89). 48.45% (n=141) of the patients were PCR (+), 51.55% (n=150) were PCR (-). 50% (n=64) of women and 47.24% (n=77) of men were PCR (+).

There was no patient need for hospitalization in the PCR (-) group. Ten of the PCR (+) patients were hospitalized, no patient needed oxygen (O_2) treatment or intensive care unit (ICU) requirement. All of 10 patients discharged in 1-week-period.

We didn't find statistically significant difference between PCR (+) and PCR (-) groups in terms of TSAT/PMJ, ASAT/PSM, LD, ASAT/ESM. A statistically significant difference was found between PCR positive and negative individuals in terms of EAT mean (p=0.007) (Table 1).

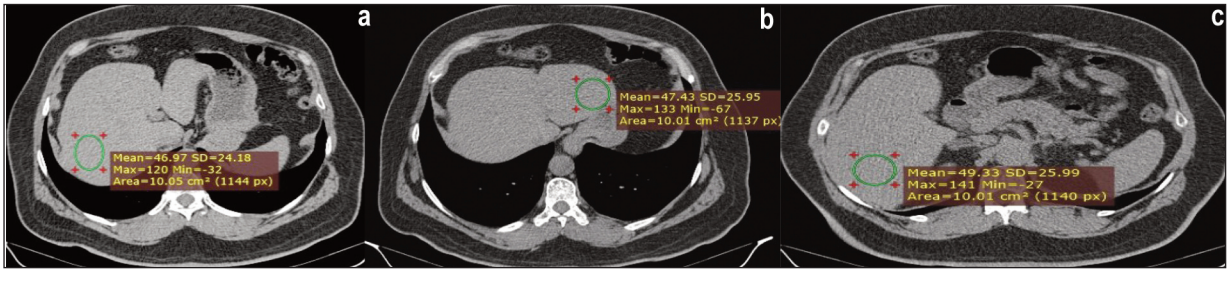

FIGURE 2: Unenhanced thorax CT of the same 51-year-old-male PCR (-) patient at abdominal sections, liver density measurement of segment **A)** 2-3, **B)** 5-8, **C)** 6-7 with a 10- cm2-freehand ROI are seen.
CT: Computed tomography; PCR: Polymerase chain reaction; ROI: Region of interest.

TABLE 1: Comparison of CT indices between PCR positive and negative patients.

CT indices	PCR (+)	PCR (-)	p value+
Liver density (hu) (mean±SD)	50.34±11.70	49.18±11.92	0.410
Epicardial adipose tissue thickness (mm) (mean±SD)	5.85±2.20	5.15±1.93	0.007
Thoracic subcutaneous adipose tissue/pectoralis major thickness (mean±SD)	1.91±1.59	1.75±1.50	0.233
Abdominal subcutaneous adipose tissue/psoas major thickness (mean±SD)	2.12±1.66	1.79±1.39	0.058
Abdominal subcutaneous adipose tissue/ erector spina thickness (mean±SD)	0.48±0.26	0.45±0.27	0.178

CT: Computed tomography; Hu: Hounsfield Unit; PCR: Polymerase chain reaction; SD: Standard deviation; mm: Millimeter; +Mann-Whitney U test. Bold values mean p<0.05.

TSAT/PMJ, ASAT/PSM and ASAT/ESM ratios were found to be statistically significantly higher in women (p=0.000, p=0.000, p=0.000, respectively). There was no statistically significant difference between LD, EAT and gender (p>0.05) (Table 2).

Statistically significant difference between PCR (+) and PCR (-) women with LD, EAT, TSAT/PMJ, ASAT/PSM and ASAT/ESM was not detected (p>0.05). While the mean EAT in men was significantly higher in the PCR (+) group (p<0.05); no significant difference was found in other CT measurements (p>0.05) (Table 3).

In PCR (+) group, LD decreased, EAT increased with increasing age (p<0.05). In the PCR (-) group, a strong positive correlation was found between EAT and age. Weak positive relationship was found between TSAT/PMJ, ASAT/PSM with age (p<0.05) (Table 4).

TABLE 2: Comparison of CT based obesity indices in terms of gender.

CT indices	Female	Male	p value+
Liver density (hu) (mean±SD)	50.76±11.98	48.94±11.64	0.154
Epicardial adipose tissue thickness (mm) (mean±SD)	5.56±2.15	5.43±2.05	0.719
Thoracic subcutaneous adipose tissue/pectoralis major thickness (mean±SD)	2.91±1.64	0.98±0.70	**0.000**
Abdominal subcutaneous adipose tissue/psoas major thickness (mean±SD)	2.71±1.78	1.35±0.95	**0.000**
Abdominal subcutaneous adipose tissue/erector spina thickness (mean±SD)	0.62±0.27	0.34±0.18	**0.000**

CT: Computed tomography; Hu: Hounsfield Unit; SD: Standard deviation; mm: Millimeter; +Mann-Whitney U test. Bold values mean p<0.05.

TABLE 3: Comparison of CT based indices in terms of gender and PCR test result.

	Female		Male	
CT indices+	PCR (+)	PCR (-)	PCR (+)	PCR (-)
Liver density (hu) (mean±SD)	50.74±13.09	50.77±10.86	50.00±10.47	48.00±12.58
Epicardial adipose tissue thickness (mm)* (mean±SD)	5.56±2.25	5.55±2.07	6.09±2.14*	4.84±1.77*
Thoracic subcutaneous adipose tissue/pectoralis major thickness (mean±SD)	2.94±1.69	2.89±1.61	1.06±0.81	0.90±0.57
Abdominal subcutaneous adipose tissue/psoas major thickness (mean±SD)	2.87±1.92	2.55±1.64	1.50±1.08	1.22±0.79
Abdominal subcutaneous adipose tissue/ erector spina thickness (mean±SD)	0.64±0.27	0.60±0.28	0.35±0.16	0.33±0.20

CT: Computed tomography; Hu: Hounsfield Unit; SD: Standard deviation; mm: Millimeter; PCR: Polymerase chain reaction; *:p<0.05; +Mann-Whitney U test.

TABLE 4: Correlation of obesity indices with PCR test result in terms of age.

Test	Liver density (hu) mean±SD		Epicardial adipose tissue thickness (mm)		Thoracic subcutaneous adipose tissue/pectoralis major thickness		Abdominal subcutaneous adipose tissue/psoas major thickness		Abdominal subcutaneous adipose tissue/erector spina thickness	
	rs	p value	rs	p value	rs	p value	rs	p value	rs	p value
PCR (+)	-0.280	**0.001***	0.450	**0.000***	-0.029	0.730	0.116	0.170	0.001	0.995
PCR (-)	-0.084	0.304	0.582	**0.000***	0.186	**0.023***	0.173	**0.034***	0.131	0.109

HU: Hounsfield Unit; cm^2: Centimeter square; SD: Standard deviation; mm: Millimeter; PCR: Polymerase chain reaction; *: p<0.05; rs: Spearman's rho.

DISCUSSION

To our knowledge, this is the first study to compare the findings of peripheral fat-muscle and visceral obesity indices in PCR positive and negative patients. While similar studies, although not exactly the same, have focused on the effects on the clinic outcome, our study reveals the importance of these findings in getting COVID-19 infection.

The most important finding in this study was the higher EAT mean in PCR (+) patients. Increase in EAT value and decreasing LD with age in the same group was another remarkable finding. There was no difference between the 2 groups in terms of fat-muscle indices and LD.

EAT is located between the myocardium and the visceral pericardium, plays a role in fatty acid metabolism like visceral fat depots and displays metabolic, thermogenic and cardioprotective effects under physiological states.[20,21] EAT can also be harmful by secreting proinflammatory cytokines like interleukin1B, 6, tumor necrosis factor.[22] Higher EAT thickness can provide increased proinflammatory cytokines in PCR (+) patients, it may create immune-dysregulation and facilitate to have COVID-19 infection.

Excess adipose tissue can cause insensitivity to leptin, deep anorexia, and a dysregulation of immune response, with an increase in susceptibility to respiratory infections.[23]

Freuer et al. found that visceral adiposity did not increase the susceptibility to have COVID-19 by measuring waist circumference and trunk fat ratio, but in our study visceral adiposity markers were LD and EAT.[24] The same study mentions as limitation that patients with mild and uncomplicated symptoms were excluded because they were not tested. Our study solves this problem by including mild and uncomplicated patients, because patients with comorbidities were not included in our study in order not to affect the measurements. Rest of the patients had mild course.

Association between the COVID-19 infection and the angiotensin-converting enzyme 2 (ACE2) receptor is reported, potentially playing a critical role in the pathological pathway.[25,26] Expression of the ACE2 receptor in visceral and subcutaneous adipose tissue is higher than lung tissue possibly explaining the higher susceptibility of COVID-19 infection in obese patients.[27,28] Although this pathway-related susceptibility has been reported to be associated with both peripheral and visceral adipose tissue, we did not observe an increased risk of detection COVID-19 with peripheral fat-muscle indices and LD. Perhaps this receptor is more abundant in EAT than in other adipose tissues.

Mahabadi et al. stated that epicardial fat (thickness or volume) plays an important role to the development and progression of CAD.[29] Epicardial adipose tissue may increase coronary events independently of risk factors such as DM, smoking, obesity and dyslipidemia.[30] Epicardial fat contains genes associated with coagulation and endothelial function.[22] Increased EAT thickness in PCR (+) patients may facilitate myocardial infarction. Endothelial dysfunction and procoagulant state caused by increased EAT in PCR (+) patients may contribute to the increase in the incidence of stroke, renal, adrenal and mesenteric ischemic conditions, pulmonary embolism, deep vein thrombosis, but long-term follow up is mandatory and not included in our study.

Iozzo et al. stated that epicardial fat has been associated with fat accumulation in the liver, however in our study, EAT was higher in the PCR (+) group, there was no difference in terms of LD, which is an indicator of fatty liver in CT.[31] Hemochromatosis, hemosiderosis, glycogen storage diseases, Wilson disease, amiodarone toxicity, gold therapy etc. can also change liver density. The fact that patients' liver diseases and medications were not included in the study may explain this dilemma in PCR (+) patients. Gualtieri et al. found increased liver density in obese and lean ICU-admitted COVID-19 patients due to glycogens synthesis and neoglucogenesis due to inflammatory state.[32] This condition may explain the LD discrepancy between 2 groups.

COVID-19 infection can affect all age groups, but more severe in older patients.[33] Higher level of proinflammatory cytokine release in elderly COVID-19 patients may lead to a severe course of the dis-

ease.[34] We found increased EAT mean and decreased LD values in PCR (+) patients by aging. As mentioned before, EAT can be associated with hepatic steatosis, increased EAT and decreased LD can lead to cytokines releasing from these visceral adipose tissues, and this state may be the reason for severe outcomes in elderly patients.[31]

Visceral adipose tissues have an important role on metabolic activity, lipolysis, and inflammatory cytokine release than subcutaneous adipose tissues, therefore we could not find a relationship between peripheral fat-muscle indices and PCR positivity in our study.[35] Peripheral fat-muscle indices may have an impact on clinical outcomes of PCR-positive moderate and severe patients, which may be revealed by future studies. Our study consisted of the mild PCR (+) patients.

Shortcomings of the study were; retrospective nature, no patients under the age of 18, BMI was not measured, the percentage of lung involvement in PCR (+) patients on CT was not included, making PSM and ESM measurements were at L1-L2 level, lack of moderate and severe patients and to exclude patients with DM, HT, CAD and malignancies. All of the patients were vaccine free, because between April-July 2020 vaccine was not used in Türkiye. EAT measurements should be supported with prospective clinical trials.

CONCLUSION

Increased EAT may facilitate having COVID-19 infection. Although peripheral fat-muscle indices do not seem to be a risk factor for getting COVID-19 infection, the correlation of these data with clinical outcomes and lung involvement rates in positive patients should be supported by future studies.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Duygu İmre Yetkin, Yeliz Çiçek;* ***Design:*** *Duygu İmre Yetkin, Yeliz Çiçek;* ***Control/Supervision:*** *Duygu İmre Yetkin, Yeliz Çiçek, Cihan Akgül Özmen;* ***Data Collection and/or Processing:*** *Duygu İmre Yetkin, Yeliz Çiçek;* ***Analysis and/or Interpretation:*** *Duygu İmre Yetkin, Yeliz Çiçek, Hıdır Sarı;* ***Literature Review:*** *Duygu İmre Yetkin, Yeliz Çiçek;* ***Writing the Article:*** *Duygu İmre Yetkin;* ***Critical Review:*** *Duygu İmre Yetkin;* ***References and Fundings:*** *Duygu İmre Yetkin, Yeliz Çiçek.*

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