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Myocardial injury in COVID-19 patients is associated with the thickness of epicardial adipose tissue

Aim	High sensitive troponin (hs-TnI) levels may increase secondary to Coronavirus disease-2019 (COVID-19), and this increase is associated with cardiovascular mortality in COVID-19 patients. Epicardial adipose tissue (EAT) is associated with myocardial injury directly as a reservoir tissue for coronavirus, and indirectly through mediators it secretes as an apocrine gland. We aimed to evaluate the relationship between myocardial injury secondary to COVID-19 infection and EAT thickness.
Material and methods	Thoracic computed tomography (CT) was performed in 73 consecutive patients diagnosed with COVID-19. EAT thickness and volume were calculated by two radiologists blind to the study data. We formed two groups according to hs-TnI concentrations, patients with myocardial damage (hs-TnI ≥11.6 ng/l) and without myocardial damage (hs-TnI<11.6 ng/dl).
Results	A total of 46 patients were women (63.0%). The mean age was 66.4±12.3 yrs in the myocardial injury group and 55.9±9.7 yrs in the group without myocardial injury (p<0.001). There were 20 hypertensive patients (68.9%) in the injury group, while there were 12 hypertensive patients (27.3%) in the group without injury (p=0.001). Glucose, C-reactive protein, D-dimer, white blood cell count, neutrophil, and neutrophil/lymphocyte ratio were higher in the injury group (p<0.05, for all variables). The mean EAT thickness was 5.6±1.6 mm in the injury group, whereas it was 4.8±1.8 mm in the group without injury (p=0.031). EAT thickness of 4.85 mm and above was associated with the myocardial injury with 65% sensitivity and 39% specificity (AUC=0.65, 95% CI: 0.52–078, p=0.031).
Conclusion	In patients with COVID-19 infection, higher rates of myocardial injury were observed as the EAT thickness increased. Epicardial adipose tissue, contributes to cytokine-mediated myocardial injury either directly or indirectly by acting as a reservoir for coronavirus. Increased EAT thickness is associated with myocardial injury in COVID-19 patients.

Keywords	COVID-19 infection; epicardial adipose tissue thickness; myocardial injury; computed tomography
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Introduction

Coronavirus-2 (SARS-CoV-2) can affect the lungs by causing acute respiratory distress syndrome. Coronavirus disease-2019 (COVID-19) can cause multiple organ involvement, including the cardiovascular system [1, 2]. In a worldwide pandemic, COVID-19 has caused significant morbidity and mortality. As the COVID-19 pandemic threatens global health, learning about the pathogenesis and clinical course of the disease can help to set therapeutic goals and to define the clinical approach.

Inflammation is a crucial factor in the development and progression of COVID-19 [3]. Studies have shown that inflammatory parameters, such as C-reactive protein (CRP), effectively predict the clinical severity of COVID-19 [4, 5]. Identifying parameters that provide information about inflammation status is essential for understanding the clinical course and prognosis of COVID-19.

Studies conducted during the pandemic have shown that obesity, especially visceral fat, adversely affects the clinical course of COVID-19 and increases mortality [6]. It has been reported that high-volume and hyper-vascularized epicardial adipose tissue (EAT) of obese patients acts as a COVID-19 reservoir that facilitates viral spread and increases the immune system response. Obesity is associated with activation of the cytokine cascade and increased production of proinflammatory cytokines, such as interleukin-6, which accelerate clinical deterioration [7].

During COVID-19 infection, the myocardium can be affected directly, or indirectly by a cytokine storm [8–10]. There may be an increase in the concentration of cardiac

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troponin, and this increase is associated with a poor prognosis in COVID-19 patients [11, 12]. However, there is not sufficient literature data about which parameters secondary to COVID-19 infection cause myocardial injury. Thus, it was considered necessary to investigate whether EAT, which is associated with an increased risk of cytokine storm secondary to COVID-19 infection, is also associated with myocardial injury. Therefore, we evaluated the relationship between myocardial injury in COVID-19 patients and EAT, as measured by thoracic computed tomography (CT).

Material and Methods

Study population

Initially included in the study were 91 patients who were hospitalized with diagnosis of COVID-19 between Jan 20 and Feb 25, 2021, and who underwent thoracic computed tomography (CT). COVID-19 was diagnosed by the positive polymerase chain reaction (PCR) test of a nasopharyngeal sample. Except for COVID-19, all other clinical conditions that might increase troponin levels were considered as exclusion criteria.

Specifically, coronary artery disease, heart failure (LVEF<50%), renal failure (eGFR<30 ml/min/1.73 m^2), poor or less than optimal image quality due to cardiac motion artifact and being under 18 years of age were exclusion criteria. Six coronary artery disease patients, three heart failure patients, two renal failure patients, and seven patients with poor image quality were excluded from the study. The study continued with the remaining 73 patients. Thoracic CT images obtained within the first two days of hospitalization were analyzed. The upper normal limit of the troponin test kit (Abbott, ARCHITECT STAT High Sensitive Troponin-I Reagent Kit) used in our laboratory was 11.5 ng/l. Patients were divided into two groups according to their hs-TnI concentration upon hospitalization, those with myocardial damage (hs-TnI ≥11.6 ng/dl) and those without myocardial damage (hs-TnI <11.6 ng/dl). The study was conducted according to the Principles of the Helsinki Declaration, and it was approved by the ethics committee of the Trabzon Kanuni Training and Research Hospital (approval number 2021/17–01). Informed consent was obtained from all patients before enrolment in the study.

Demographic and laboratory data

The patients' demographic data, daily drug use, and laboratory data were collected from the hospital's data system and recorded. Laboratory data, including CRP, hs-TnI, glucose, complete blood count, kidney function test, and D-dimer values, were analyzed.

Thoracic CT

CT was performed for each patient using a 128-slice scanner (General Electric, Revolution EVO, USA) in the supine position at end-inspiration. A low-dose CT protocol was applied, using 0.5 sec gantry rotation time, 0.625 mm×64 detector array, 1.375 mm/s pitch, table speed/rotation, 80 mA, 100 kV, and 512×512 matrix parameters. ASIR was on, and the Auto mA scan parameter was off. A slice thickness of 0.625 mm and a reconstruction range of 0.625 mm were used for sagittal and coronal image reconstruction. Passive air ventilation was performed for at least 30 min after each CT imaging, and the machine surfaces were disinfected with ethanol and didyldimethylammonium chloride (DDAC).

CT data in DICOM format were transferred to a picture archiving and communication system (PACS). All CT images were viewed in axial, sagittal, and coronal planes. Two experienced radiological specialists, blind to the study data, interpreted the thoracic CT images. If the two radiologists could not make a joint decision about the measurements, a third opinion was obtained.

Cardiac index dimensions were obtained from the thoracic CT scans. Thorax CTs were evaluated from the mediastinal window. Epicardial fat was defined as the adipose tissue extending from the visceral epicardium to the outer edge of the myocardium. EAT thickness was evaluated by measuring the distance from the visceral epicardium to the myocardium in the axial plane (Figure 1).

Volume Viewer software (Advance Work Station (ADW) version 4.7) with Linux software was used to partition and analyze the volumes to be studied. Then, CT volumes (in DICOM format) were uploaded to the software. The regions other than epicardial fat were removed according to the Hounsfield Unit (HU) scale using the Threshold tool. For the determination of adipose tissue, the lowest density range used was -250 to -190, while the highest density range was -30 to -50 [13]. The total volume of EAT (EATv) was calculated (Figure 2). The data recorded in the Summary Table application of the software were used to interpret the information obtained in the Volume Viewer and to organize the measurements related to the patients.

Statistical analysis

The Statistical Program for Social Sciences (windows 20; SPSS Inc, Chicago, USA) was used for all statistical calculations. Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test and are presented as mean±standard deviation. Categorical variables were expressed as percentages. Since EAT, EATv, troponin, creatinine, and WBC data were not normally distributed, Mann–Whitney U tests were used to compare between group means. The other continuous variables were normally distributed, and Student t-tests were used for their analysis.

Figure 1. Measurement of EAT thickness in the axial plane by CT

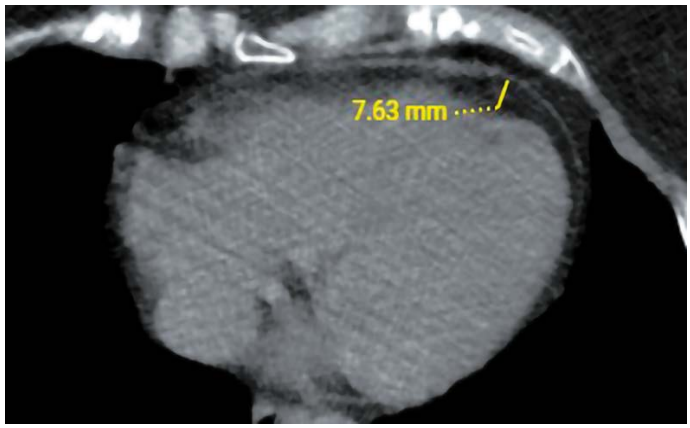
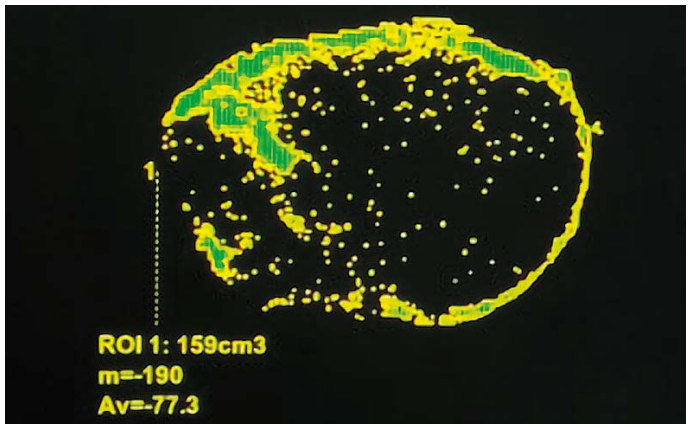


Figure 2. Measurement of EATv by CT



The Chi–Square test was used to determine differences between groups of categorical variables. Spearman correlation analyses were used to determine the correlation between troponin and EAT values. The capacity of EAT values for predicting myocardial injury was analyzed by Receiver Operating Characteristics (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity and specificity values are presented. A p value less than 0.05 was considered statistically significant.

Table 1. Demographic and laboratory data of patient groups with and without myocardial injury

Variables	Group with myocardial injury (n=29)	Group without myocardial injury (n=44)	p, value
Age	66.4±12.3	55.9±9.7	<0.001
Female gender	22 (75.8)	24 (54.5)	0.065
BMI, kg/m^2	31.3±4.8	29.9±4.8	0.204
Hypertension	20 (68.9)	12 (27.3)	0.001
Diabetes mellitus	5 (17.2)	2 (4.5)	0.071
Smoking	1 (3.4)	5 (11.4)	0.228
ASA	5 (17.2)	0 (0.0)	0.004
ACE inhibitor	9 (31.0)	5 (11.4)	0.037
ARB	5 (17.2)	4 (9.1)	0.300
Diuretics	12 (41.4)	5 (11.4)	0.003
Beta blocker	6 (20.7)	1 (2.3)	0.009
CCB	5 (17.2)	4 (9.1)	0.003
Glucose, mg/dl	146±60	121±33	0.025
Creatinine, mg/dl	0.9±0.2	0.85±0.2	0.444
CRP, mg/l	80.2±93.7	22.8±40.6	0.001
Troponin, ng/l	56.6±12.4	3.9±2.1	0.006
D-dimer, mg/dl	612±577	214±205	<0.001
WBC, x10^3/μl	8.5±4.5	6.5±2.9	0.022
Hb, g/dl	13.1±1.4	13.5±1.8	0.371
Plts, x10^3/μl	230±88	211±78	0.566
Neutrophyls, x10^3/μl	6.5±4.5	4.2±2.6	0.008
Lymphocytes, x10^3/μl	1.3±0.69	1.7±0.66	0.152
NLR	8.06±1.9	3.25±0.39	0.004
EAT, mm	5.6±1.6	4.8±1.8	0.031
EATv, cm^3	134±33	133±37	0.706

Data are mean±SD or n (%). ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CRP, C reactive protein; WBC, white blood cell count; Hb, hemoglobin; Plts, platelets; NLR, neutrophil-lymphocyte ratio.

Results

Demographic and laboratory data are presented in Table 1. The mean age of patients with myocardial injury was 66.4±12.3 yrs, and the mean age of those without injury was 55.9±9.7 yrs (p<0.001). There were 20 (68.9%) hypertensive patients in the injury group, whereas there were 12 (27.3%) hypertensive patients in the group without myocardial injury (p=0.001). Blood glucose in the injury group was higher than the group without myocardial injury (p=0.025). CRP level was 80.2±93.7 mg/l in the injury group and 22.8±40.6 mg/l in the group without myocardial injury (p=0.001). The neutrophil-lymphocyte ratio (NLR) was higher in the group with myocardial injury (p=0.004). Blood serum troponin level was 56.6±12.4 ng/l in the injury group and 3.9±2.1 ng/l in the group without myocardial injury (p=0.006). D-dimer, white blood cell (WBC), and neutrophil values were higher (p<0.001, p=0.022, p=0.008, respectively) in the group with myocardial injury (Table 1).

The mean EAT thickness was 5.6±1.6 mm in the injury group and 4.8±1.8 mm in the group without myocardial injury (p=0.031). EAT thickness was positively correlated with troponin (r=0.3, p=0.009). ROC analysis demonstrated that EAT thickness of 4.85 mm and above was associated with myocardial injury with 65% sensitivity and 39% specificity (AUC=0.65, 95% CI: 0.52–0.078, p=0.031; Figure 3). EAT thickness was also positively correlated with BMI (r=0.34, p=0.005). EATv values did not differ between the groups.

Discussion

This study provided new information about the relationship between EAT thickness obtained from thoracic CT

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images and myocardial injury in hospitalized COVID-19 patients. We found a positive correlation between the EAT thickness and myocardial injury. This result suggests that attention should be paid to the EAT thickness in thorax CT performed on COVID-19 patients.

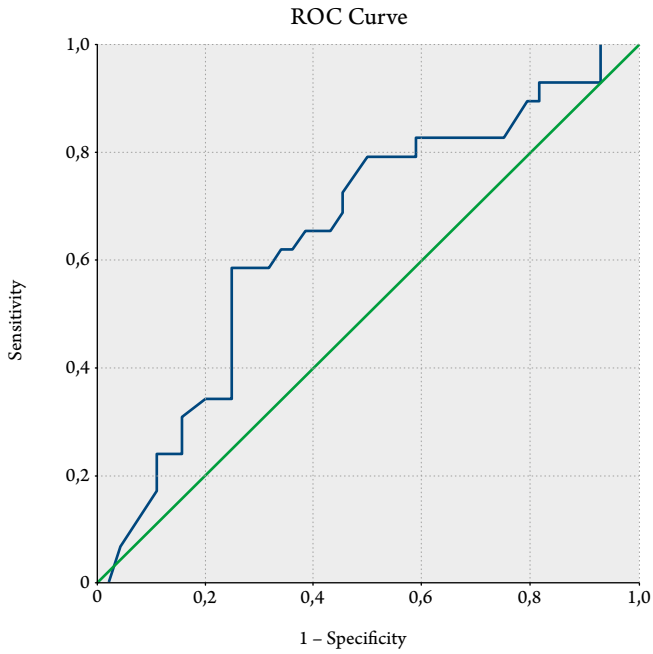
Inflammation is vital in the development and progression of COVID-19 [3]. Studies have shown that inflammatory parameters, such as C-reactive protein (CRP), effectively predict the clinical severity of COVID-19 [4, 5]. It has been reported that leukocyte and neutrophil counts and the NLR can be used as markers of advanced disease in COVID-19 patients [14–16]. In the present study of COVID-19 patients, higher values of CRP, leukocyte, neutrophil, and NLR were found in the group with myocardial injury. Identifying parameters that give information about inflammation is essential in determining the clinical course and prognosis of the disease.

EAT is located between the myocardium and the visceral pericardium, and it is a fat depot that has systemic and local physiological effects [17]. An increase in EAT is associated with coronary artery disease, atrial fibrillation, metabolic syndrome, and hypertension [17]. In recent studies, obesity has been shown to be an independent risk factor for COVID-19 complications, and ectopic and visceral fat deposits have been reported to be new indicators of this risk [18]. This study found that an increase in EAT was correlated with the severity of the COVID-19 infection [18].

A meta-analysis showed that increased troponin correlated with COVID-19 severity and mortality [19]. Increased troponin concentrations are frequently encountered during hospitalization of patients with COVID-19, and high troponin is associated with myocardial injury and fatal outcomes [19, 20]. Mechanisms that cause myocardial injury secondary to COVID-19 infection have not been delineated. Suggested potential mechanisms that cause myocardial injury include direct myocardial injury mediated by angiotensin-converting enzyme 2 (ACE2), damage secondary to hypoxia, microvascular damage, and systematic inflammatory response syndrome [21, 22].

COVID-19 infection becomes active by binding to ACE2 receptors that are present in large amounts in the heart and lungs [23]. Studies have shown that down-regulation of the myocardial ACE2 system can cause myocardial inflammation [23], and the decrease in ACE2 has been associated with inflammation of EAT. The presence of elevated ACE2 in EAT, which is a visceral fat store, increases the importance of EAT in myocardial inflammation [23]. Large amounts of ACE2 and inflammatory cytokines, tumor necrosis factor-a (TNF-a), and interleukin-6 (IL-6) are found in EAT [24]. Inflammatory factors such as TNF-a and IL-6 decrease cardiac inotropic effects and function. Therefore, TNF-a and IL-6 cause increased systemic hypoxia and myocardial inflammation [17, 24]. The imbalance between anti and pro-inflammatory adipokines released from EAT may play a role in the formation of a cytokine storm [25]. These findings show that EAT plays a key role in the myocardial injury that may develop in COVID-19 patients due to ACE2 and a cytokine storm.

Figure 3. ROC analysis of EAT tissue thickness and myocardial injury



Diagonal segments are produced by ties.

EAT thickness can be calculated quickly and precisely by the high 3-dimensional resolution of thoracic CT [26]. The intensive use of CT during the COVID-19 pandemic has made it more available to evaluate potential prognostic parameters of COVID-19, such as EAT thickness. An increase in EAT thickness is an essential, independent predictor of adverse cardiac events and survival [27–30]. Myocardial injury secondary to COVID-19 infection is a common complication and is associated with an increased risk of acute coronary syndrome, cardiogenic shock, and heart failure [31–33].

Cardiac disorders that may develop after COVID-19 infection are associated with an increased risk of mortality [34]. Therefore, it is of paramount importance to identify, treat, and provide special care to avoid potential adverse events in patients at high risk of myocardial injury secondary to COVID-19 infection. In the present study, we investigated the relationship between myocardial injury secondary to COVID-19 infection and EAT thickness, which is an inflammation parameter. We found that the increase in EAT thickness in COVID-19 patients was associated with a higher rate of myocardial injury. Although the mechanism responsible for the development of myocardial injury

associated with mortality in COVID-19 patients has not been determined precisely, it should be considered that EAT thickness, which can be easily measured by thoracic CT, is associated with myocardial injury. The current observation that higher rates of myocardial injury accompany increased EAT thickness suggests that EAT thickness can be used as a guide for preventing or treating this injury. Further research is needed to confirm the hypothesis that EAT thickness is a predictor of myocardial injury.

Limitations

The present study was performed at a single center, and the number of patients included was relatively low. The cross-sectional design of the study is also a limitation. The relationship between the development of myocardial injury and EAT thickness in patients with COVID-19 infection was evaluated.

However, the lack of control data on EAT thickness in patients with similar demographic characteristics who had no COVID-19 infection is a limitation. Additionally, excluding patients with comorbidities known to cause an increase in troponin levels limits the application of the results to large populations. We cannot exclude potential effects of this lack of comorbidity data on our conclusions.

Conclusions

A positive correlation was found between the risk of myocardial injury and EAT thickness in patients with COVID-19. Since, myocardial damage has been shown to be associated with increased mortality in COVID-19 patients, it is recommended that EAT thickness be evaluated from routine thoracic CT images.

Informed consent

The study protocol was approved with registration number of 2021–17/01 by the Trabzon Kanuni Training and Research Hospital ethics committee.

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No conflict of interest is reported.

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