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Research Article

Subcutaneous Adipose Tissue Attenuation as Marker of Prognosis in Patients Admitted with Covid-19

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Abstract

Objective: To investigate the association of Computed Tomography (CT) Subcutaneous Adipose Tissue (SAT) attenuation with outcome in patients admitted due to SARS-CoV-2 infection.

Background: Obesity is associated with worse outcomes in coronavirus disease 2019 (COVID 19) but the underlying mechanisms are not well known. It is thought that the adipose tissue promotes a proinflammatory state that affects negatively these patients.

Methods: We retrospectively analyzed chest CT scans of 75 patients admitted for SARS-CoV-2 infection. SAT attenuation was measured. Clinical and prognostic variables were collected from the medical reports. A statistical analysis was performed to determine the association of SAT attenuation CT measurements with the prognosis of COVID 19.

Results: Mean age of patients was 71 years and 56% were male. Comorbidities included hypertension (54.7%), cancer history (27%), diabetes mellitus (25%) and obesity (8.7%). During admission 10 patients required intensive care (13.3%), all of them with mechanical ventilation and 7 patients needed vasopressor support (9.3%). In-hospital mortality occurred in 18 patients (24%). SAT attenuation was higher in hypertensive patients (-106.3±14.4 *vs.* -114.7±13.4 HU, p=0.011) in patients with cancer history (-102.6±13.8 *vs.* -112.8±13.9 HU, p=0.006 and in patients who died (-99.9 *vs.* -113.3 HU, p<0.001).

Conclusion: SAT attenuation was associated with death in admitted patients with COVID-19. SAT attenuation is a broadly available marker that may indicate poor prognosis in COVID-19 patients.

Keywords: Computed tomography; Subcutaneous adipose tissue; Coronavirus disease

Abbreviations

COVID-19: Coronavirus Disease 2019; SAT: Subcutaneous Adipose Tissue; CT: Computed Tomography; HU: Hounsfield Units; BMI: Body Mass Index; IQR: Interquartile Range

Introduction

The disease caused by the new coronavirus SARS-CoV2 spread rapidly in 2020 throughout the world, causing a global pandemic with high mortality [1]. More than a year later, we are still immersed in it and researchers continue working hard to identify the most vulnerable patients. Several studies have reported that obesity increases the risk of COVID-19 morbidity and mortality, especially among young adults [2-9]. However, all obese patients do not have the same response to the disease and we have to look beyond the body mass index and the amount of subcutaneous adipose tissue (SAT) if we really want to understand the mechanisms implied [10]. Chest computed tomography (CT) examination is often used to assess COVID-19 patients, however prognostic parameters beyond pulmonary affection have not been investigated yet. Besides the obvious lung evaluation, chest CT allows to quantify adipose tissue and to assess its metabolic activity. CT imaging can differentiate tissue subtypes by measuring radiodensity or attenuation with a quantitative scale, referred to as Hounsfield units (HU). In the particular case of adipose tissue, CT fat attenuation provides a non-invasive and indirect measure of fat composition and quality: Adipose tissue with relatively lower lipid content and higher vascularity has less negative (higher) Hounsfield units (HU) because the increased extracellular matrix [11]. Furthermore, CT attenuation can distinguish the metabolic activity of the adipose tissue; highly active adipose tissue will have more positive HUs, and hence greater tissue densities [12], which has been previously related to proinflammatory states.

The purpose of this study is to investigate the association of SAT attenuation with prognostic markers in patients with COVID-19 admitted to the hospital.

Methods

We retrospectively included 75 patients admitted at our hospital due to COVID-19 infection who underwent chest CT. The decision to perform the CT was made clinically, according to the responsible physician criteria. The study was performed in accordance to the institutional review board of our center.

Body mass index (BMI) was calculated as weight in kg/height in

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Figure 1: Adipose tissue segmentation and fat attenuation evaluation.

m2. Patients were considered overweighted if BMI was 25-29.9 kg/m^2 and obese if BMI was ≥30kg/m^2. Clinical data were prospectively collected in a dedicated database during patients' admission.

Computed Tomography analysis of adipose tissue distribution

CT images were analyzed in a dedicated Corelab (ICICORELAB) using a state-of-the-art workstation tool (AW Server, General Electric Healthcare®, Massachusetts, USA). SAT attenuation was measured in a single region of interest in the back, to avoid any interference from the mammary tissue (Figure 1).

Statistical analysis

Categorical variables are reported as number (percent) and continuous variables as mean ± standard deviation or median [25^{th} to 75^{th} interquartile range], depending on variable distribution. Group comparisons were analysed with the Student t test or Wilcoxon rank-sum test for numeric variables and the χ^2 or Fisher exact test for categorical variables. Correlations between continuous variables were assessed using Pearson correlation coefficients. All analyses were conducted using the statistical software IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp. USA. Differences were considered statistically significant when p value was <0.05.

Results

We included 75 consecutive patients who were admitted with COVID-19 at our hospital and underwent a chest-CT between March and May 2020. The main baseline characteristics of the study cohort have already been reported in a previous study [13] and are summarized in Table 1.

Patients had a mean age of 71±11 years (range: 42-96) and 56% of them were male. Median in-hospital stay was 15 days [interquartile range: 8-30, range: 1-64]. Most patients (91%) received treatment with hydroxychloroquine and antibiotics and 71% with steroids. Ten patients were critically ill and required mechanical ventilation. We documented 18 deaths (24%).

Mean SAT attenuation was -110 ± 14 HU. We found a weak positive correlation between SAT attenuation and age (r=0.23, p=0.047). SAT attenuation was higher in hypertensive patients (-106.3±14.4 *vs.* −114.7±13.4 HU, p=0.011) and in patients with cancer history (-102.6±13.8 *vs.* -112.8±13.9 HU, p=0.006). Regarding the clinical outcome, SAT attenuation was higher in those patients who died during admission (-99.9±16 *vs.* -113.3±12.5 HU, p<0.01).

Table 1: Baseline characteristics of the 75 patients.

Age	71±11 years
Male	42 (56%)
Comorbidities	
Hypertension	41 (55%)
Diabetes mellitus	19 (25%)
Smoker	
Never smoked	46 (61%)
Former smoker	23 (31%)
Active smoker	6 (8%)
Chronic ischemic cardiac disease	10 (13%)
Chronic kidney disease	7 (9%)
Malignancies	20 (27%)
Obesity	
Normoweight	29 (38.7%)
Overweight	32 (42.7%)
Obesity	14 (18.7%)
Chronic treatment	
Statins	31 (41%)
Angiotensin-converting-enzyme inhibitors	28 (37%)
Steroids	12 (16%)
Oral anticoagulation	9 (12%)
Laboratory results	
Leukocyte count, × 10^9/L	8 093.87 ± 6 169.118
Lymphocyte count, × 10^9/L	1 117.03 ± 715.736
Haemoglobin, mg/dL	12.7 [11-14]
D-dimers, ng/mL	1 242 [534-3 860]
C-reactive protein, mg/L	70 [37-146]
Troponin, ng/L	14.3 [8-24.7]
In-hospital treatment	
Hydroxychloroquine	68 (91%)
Antibiotics	68 (91%)
Steroids	53 (71%)
Colchicine	16 (21%)
Ciclosporine	6 (8%)
Clinical complications	
Mechanical ventilation	10 (13%)
Intensive care admission	10 (13%)
Vasopressors required	7 (9%)
Septic shock	9 (12%)
Bacterial co-infection	23 (31%)
Thromboembolic event	12 (16%)
In-hospital death	18 (24%)

Categorical variables are expressed as n (%). Continuous variables are expressed as mean±standard deviation or median [IQR].

We also found a non-significant trend towards a higher attenuation in patients presenting a bacterial coinfection (- 105.4±16.03 *vs.*

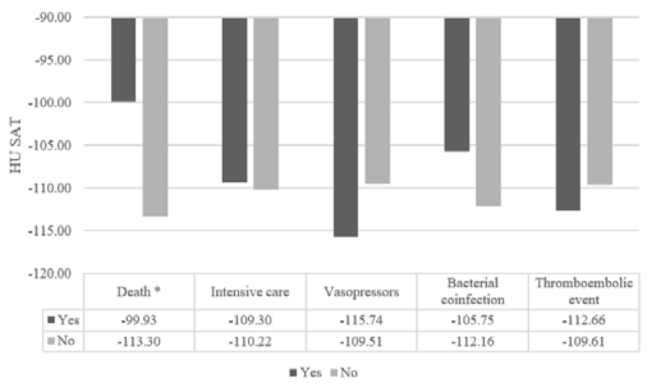

Figure 2: Relationship between SAT attenuation and prognosis (HU SAT: Hounsfield Units in the subcutaneous adipose tissue. *p<0.005).

Table 2: Variables associated with mortality.

	Dead (n=18)	Alive (n=57)	p-value
Age (years)	77 ± 10	69 ± 11	0.01
Hypertension	14 (78%)	27 (47%)	0.024
Dyslipidemia	12 (67%)	22 (39%)	0.037
Cancer	9 (50%)	11 (19%)	0.015
Obesity	9 (50%)	37 (65%)	0.257
Hemoglobin (mg/dl)	11.2 ± 1.7	12.7 ± 2.3	0.012
White cell count (10^9/L)	9215 [7100-12430]	5910 [4470-9010]	0.036
Lactate dehydrogenase (U/L)	356 [307-516]	287 [210-352]	0.017
D-dimers (ng/mL)	1853.50 [1269-4547]	994 [520-2698]	0.04
Troponin (ng/L)	40.4 [13-102]	12.8 [8-18]	0.034
C-reactive protein (mg/L)	139 [121-199]	61.5 [31-123]	0.009
SAT attenuation (UH)	-99.9 ± 16	-113.3 ± 12	<0.001

-112.16±13 HU, p=0.063) (Figure 2).

Variables related with mortality

Main factors associated with higher mortality in the univariate analysis have been previously reported [13] and are summarized in Table 2. SAT attenuation was statistically associated with higher in-hospital mortality. Other clinical factors included age, hypertension, dyslipidaemia, and prior cancer. Finally, laboratory parameters associated with mortality included baseline haemoglobin, total white cell count, D-dimers, troponin, C-reactive protein, and lactate dehydrogenase levels. We didn´t find an association between obesity and mortality.

Discussion

In our cohort of patients, SAT attenuation was significantly higher in patients who died during admission.

Obesity has been related to mortality in patients with COVID-19 [4,6,9,14]. As our knowledge of obesity improves, it is becoming more common to broaden the study beyond the BMI and to include other parameters such as the location of the fat deposits, the total amount of fat in these deposits and the metabolic activity of the tissue [15,16]. Several studies have identified fat attenuation as a marker of poor prognosis in different scenarios; in a large cohort from the Framingham Heart Study they found an increase in the multivariable-adjusted risk of all-cause mortality in patients with higher HU in both visceral adipose tissue and SAT [17].

Our study suggests that in COVID-19 patients, subcutaneous adipose tissue activity but not obesity is associated with prognosis. There is strong evidence showing that obesity is associated with a worse prognosis in COVID-19 patients [2-9], however we failed to find an association between obesity and mortality. Most of the studies in obesity show that the increased risk affects mainly to those with severe obesity (type 3 and morbid conditions) and specially to young patients. Our patients were old (more than 75% of our population was older than 65 years-old) and mainly overweighted. Only 20% of our patients were obese and there was only one patient with type 3 obesity and none with morbid obesity. Due to this particular demographic features an association between obesity and mortality was not found in our study. However, we have found an association between SAT attenuation and mortality: patients who died presented higher HU values in SAT than patients who survived. Due to the small number of deaths within the population (18 patients) we did not perform a multivariable analysis to explore whether this finding is just a marker of poor prognosis or an independent predictor of mortality in COVID patients, in fact, SAT attenuation was also higher in older patients and among those with cancer history and hypertension. All these clinical factors were also associated with a higher mortality in the univariate analysis. Therefore, our findings must be interpreted as hypothesis generators. They suggest that the metabolic activity of the subcutaneous fat is increased in patients who die of COVID and they show that fat attenuation could be a radiological marker useful in the clinical practice to identify patients with higher risk. The advantages of this parameter are that it is easy to measure and do not require a specific acquisition, so it can be widely used in clinical practice. Our findings reinforce the concept that adipose tissue plays a role in COVID-19 severity and that this role is related with inflammation.

To our knowledge the relationship between SAT attenuation and complications or mortality has not been reported previously. Pranata et al [18] have published a systematic review including five studies that analyze the relationship between visceral and subcutaneous fat areas and severe COVID 19 disease (understood as disease progression, ICU admission or need of mechanical ventilation). They concluded that a higher visceral fat area was associated with severe COVID 19. However, they didn’t find any association with subcutaneous adiposity.

Other interesting publication by Yang et al [19] analyzed intramuscular fat deposition in 143 patients with COVID 19 disease. Those with lower attenuation of the skeletal muscle in computed tomography (indicating a high intramuscular fat content) presented an increased risk of critical illness, mechanical ventilation and death. Epicardial and visceral attenuation was studied in a cohort of 65 young patients in Wuhan but no relationship with prognosis was found [20]. Finally, Iacobellis et al (REF) have also studied epicardial and succutaneous fat inflammation in COVID patients. They found that patients with severe and critical COVID-19 had significantly greater epicardial adipose tissue attenuation than those presenting with mild and moderate COVID-19, but a relationship between SAT attenuation and complications or mortality was not seen either [21].

Our study presents several limitations. First, the number of patients included is small, this prevented us to perform a multivariate study to determine the nature of the associations found. Second, our design was retrospective, which limits causal inference of our findings; admitted patients were not systematically included, they were selected by their physicians´ criteria to undergo a chest CT which implies a significant selection bias. Third, there was not a unified CT protocol. The exam performed was determined by the radiologist in charge.

Conclusion

SAT attenuation is higher in patients who died during admission. This parameter is broadly available and easy to measure in routine CT-scans to better characterize the prognosis of COVID-19 patients.

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