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ORIGINAL ARTICLE

Cut-off point of CT-assessed epicardial adipose tissue volume for predicting worse clinical burden of SARS-CoV-2 pneumonia

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Abstract

Objective To identify a cut-off value of epicardial adipose tissue (EAT) volume quantified by CT associated with a worse clinical outcome in patients with SARS-CoV-2 pneumonia.

Materials and methods In this retrospective study, sixty patients with a diagnosis of laboratory-confirmed COVID-19 pneumonia and a chest CT exam on admission were enrolled. Based on a total severity score (range 0–20), patients were divided into two groups: ordinary group (total severity score < 7) and severe/critical group (total severity score > 7). Clinical results and EAT volume were compared between the two groups.

Results The severe/critical patients, compared to the ordinary ones, were older (66.83 ± 11.72 vs 58.57 ± 16.86 years; $p = 0.031$), had higher body mass index (27.77 ± 2.11 vs 25.07 ± 2.80 kg/m^2; $p < 0.001$) and higher prevalence of comorbidities. EAT volume was higher in severe/critical group, compared with the ordinary group (151.40 ± 66.22 cm^3 vs 92.35 ± 44.46 cm^3, $p < 0.001$). In severe/critical group, 19 (73%) patients were admitted in intensive care unit (ICU), compared with 6 (20%) patients in the ordinary group ($p < 0.001$). The area under the ROC curve (AUC) is equal to 0.781 ($p < 0.001$) (95% *CI*: 0.662–0.900). The cut-off found, in correspondence with the highest value of the Youden Index, is 97 cm^3: the sensitivity is equal to 83.3%, while the specificity is equal to 70% for predicting a worse outcome. The risk (odds ratio) of belonging to the severe/critical group in this population due to $EAT \geq 97$ cm^3 is 11.667 (95% *CI*: 3.384–40.220; $p < 0.001$).

Conclusion An EAT volume of 97 cm^3 has good sensitivity and specificity to predict a greater extent of pulmonary involvement and therefore a worse clinical outcome in patients with SARS-CoV-2 pneumonia.

Keywords EAT volume · SARS-CoV-2 pneumonia · Total severity score · ICU admission

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause serious illness requiring hospitalization in a minority of cases, with 5–8% of cases subsequently admitted to intensive care unit (ICU) [1]. In susceptible individuals, the virus causes a powerful response, leading to hyperinflammation and cytokine storm syndrome [2].

Early identification of severe/critical cases is of paramount importance to implement successful treatment that can reduce complications and mortality [3].

Obese patients may be more susceptible to SARS-CoV-2 infection, and infected patients should be carefully monitored for adverse outcomes [4]. Obesity has been shown to increase the risk of hospitalization, ICU admission, IMV requirement, and death among patients with COVID-19 [5, 6]. A higher body mass index was associated with ICU admission and critical illness [7, 8]. Furthermore, excessive visceral adiposity appears to be associated with severe COVID-19 outcomes [9].

CT-derived EAT volume measurements are correlated with abdominal visceral adiposity and metabolic risk factors. Epicardial adipose tissue (EAT), the visceral adipose tissue

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of the heart located between the myocardium and the visceral layer of the pericardium, is an active endocrine organ that is a potential source of inflammatory mediators. In previous studies, it has been shown that increased EAT volume is associated with both decreased lung function in healthy individuals and increased disease severity in patients with chronic lung disease [10, 11]. Recent studies have advanced the potential role of EAT as a risk factor for myocardial inflammation in COVID-19 patients [12, 13]. Recently, EAT has also been proposed to be independently associated with the extent of pneumonia and adverse outcomes in patients with COVID-19 [14].

Therefore, the purpose of this study was to define an EAT volume cut-off point, measured by CT, to predict adverse outcomes in COVID-19 patients.

Methods and materials

Patient population

A total of 60 consecutive patients diagnosed with COVID-19 pneumonia (mean age 66.83 ± 11.72 years; 78% male; body mass index 26.4 ± 5.7, were retrospectively included in our study.

Confirmed diagnosis was defined as a positive result to RT-PCR (real-time polymerase chain reaction) assay for SARS-CoV-2 nucleic acid in throat swabs or lower respiratory tract associated with the characteristic radiological findings indicative of COVID-19 pneumonia. Only patients who underwent CT scan at hospitalization and who had characteristic COVID-19 findings on CT scan were included in the study. Patients admitted for other reasons and subsequently diagnosed with overlapping SARS-CoV-2 infection were excluded. In addition, the exclusion criteria were as follows: patients with no CT manifestations of pneumonia but with a positive RT-PCR result, pneumonia caused by bacteria or other common viral pathogens, chest CT with degradation movement artifacts, pathological history of lung surgery, history of lung cancer.

All patients were divided into two groups based on a previously proposed CT total severity score cut-off [15]. The two groups were compared in terms of demographics, comorbidities, and EAT volume. We also examined the association between EAT volume and ICU admission.

Chest CT protocol

Chest CT was performed with a 64-slice CT scanner (Philips Brilliance). Scanning parameters were as follows: collimation 64 × 0.6 mm; tube voltage 100 – 120 kV; tube current 110 – 280 mA, pitch 1.0, and matrix size 512 × 512. CT images were reconstructed in the transverse plane with 1.0-mm slice thickness and 1.0-mm increment. Images were also reconstructed in coronal and sagittal planes with 3.0-mm slice thickness.

Pulmonary lobe-based quantitative visual assessment of CT images

CT image data were used for visual analysis of COVID-19 pneumonia lobe extension. A single reader reviewed all the chest CT features using both axial CT images and multiplanar reconstruction images. For each of the 60 patients, CT images were evaluated for presence of ground-glass opacity (GGO), reticulation from intralobular/interlobular septal thickening, crazy-paving pattern and consolidations. In order to quantify lung lesions, a score proposed in a previous study was used [15]. Each of the lung lobes was assigned a score based on involvement, classified as follows: none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%); the corresponding scores were 0, 1, 2, 3, and 4, respectively. All five lobar scores were summed with a possible total severity score from 0 to 20.

Based on the cut-off value proposed by previous study, patients were divided into 2 groups: ordinary cases and severe/critical cases: when the total severity score was above the cut-off value of seven (7), patients were included in the severe/critical group; below this value, patients were included in the ordinary group [15].

Volumetric quantification of EAT volume

Epicardial adipose tissue (EAT) volume was considered as the fat between the surface of the myocardium and the visceral layer of the pericardium. As proposed previously [16], the total epicardial adipose tissue was measured from mediastinal window by manually tracking countours of the pericardium on the 1.0-mm-thick axial images, in every 4th slice, from a cranial level passing through pulmonary artery bifurcation to the apex of the heart caudally. Countours were then interpolated and traced the parietal pericardium in all slices interposed between the manually traced slices. Within the region of interest, fat voxels were identified using threshold attenuation values of – 30 to – 190 HU. EAT volume was automatically calculated by the software program from 3-dimensional fat voxels and reported in cm^3. All epicardial fat measures were performed by a single operator. Then all images were reviewed and interpreted on PACS workstations (Fig. 1). EAT volume was measured for all patients using a computer-aided evaluation software (Syngo.via, version VB10A; Siemens Healthcare, Erlangen, Germany).

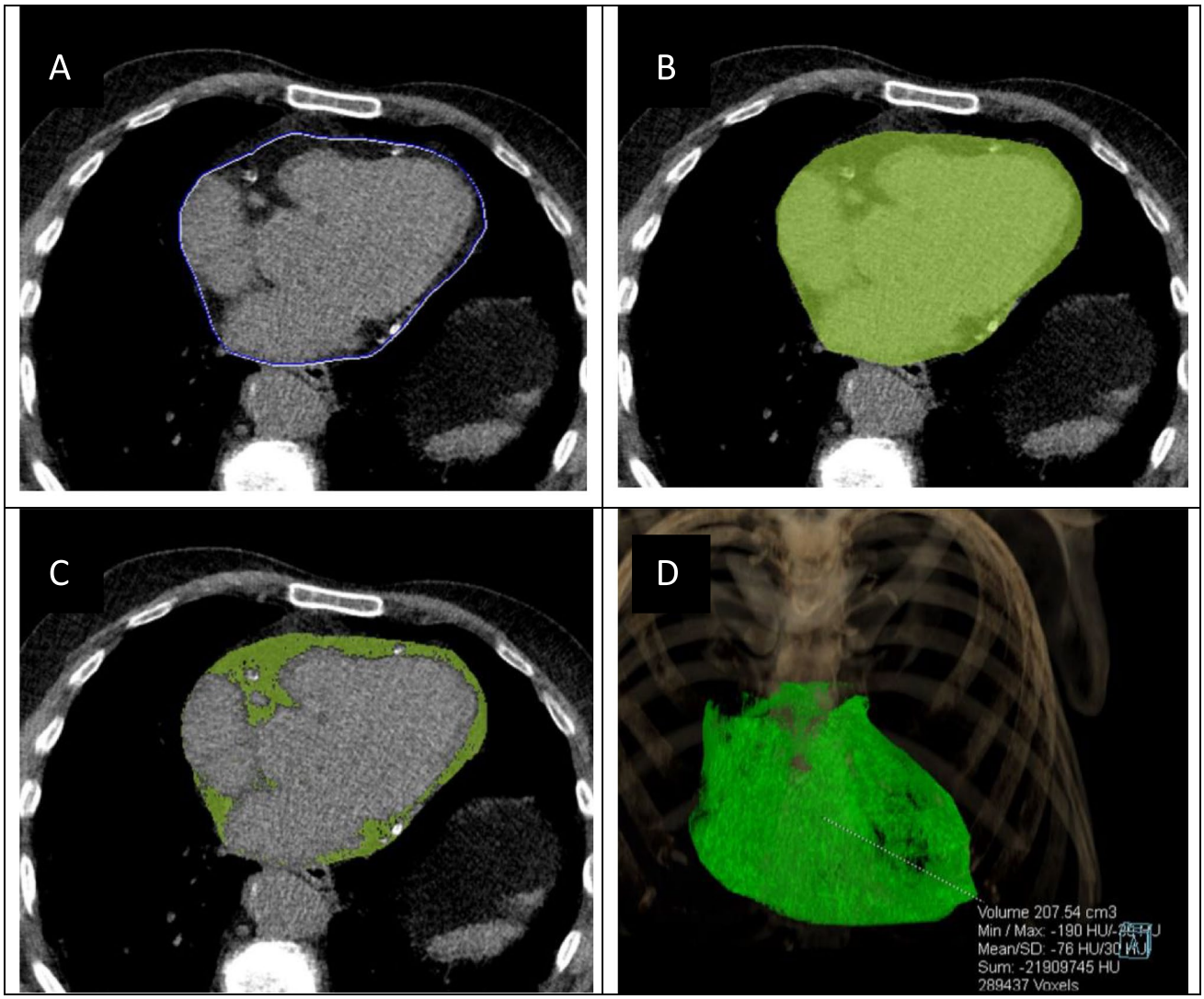


Fig. 1 EAT semi-automated quantification. **A** At each 4th axial slice the reader manually traced the pericardium. **B** Pericardial contours were then automatically generated between the user-defined pericardial linings. **C** The threshold-based software algorithm detected and quantified all fat voxels within the pericardial contour to generate EAT, using a predefined threshold of − 190 to − 30 HU to identify fat voxels. **D** Three-dimensional image of epicardial fat interpolated using a threshold-based software algorithm. EAT volume is highlighted in green color

Statistical analysis

Statistical analysis was performed with the SPSS 25 software (Statistical Package for the Social Sciences; Chicago, IL, USA) and $p < 0.05$ indicated a statistically significant difference. Continuous variables were expressed as the mean ± SD, and discrete variables were expressed as absolute numbers and percentages. Pearson's chi-square test was conducted to verify if a statistically significant association was between the membership group and each categorical variable and, if so, the intensity of the association was calculated using the Cramer V statistic. The Mann–Whitney *U* test was used to check for differences between the quantitative variables in the two groups and to test the difference between EAT volume values in the ICU admission and IMV groups. The ROC curve was used to determine the EAT volume cut-off. The area under the curve (AUC) of 1 was considered optimal, while an AUC of less than 0.5 was considered of poor validity. The Youden index was used to determine the optimal cut-off point from the ROC curve, calculated with the formula $YI = (\text{sensitivity} + \text{specificity}) - 1$. The risk (odds ratio) of being in the severe/critical group or not was determined using the obtained EAT volume value. With a logistic regression, it has been shown how the probability of belonging to the severe/critical group

changes for high values of EAT volume. Pearson's chi-square test was used to verify the association between EAT volume and ICU admission.

Results

Patients' characteristics

A total of 60 patients with laboratory confirmed COVID-19 who underwent chest CT on admission to hospital were included.

The severe/critical group consisted of 30 subjects, 80% males and 20% females, with a mean age of 66.83 ± 11.7 years, mean BMI of 27.77 ± 2.1 kg/m^2 and mean total severity score of 15.00 ± 2.2. The ordinary group consisted of 30 subjects, 77% males and 23% females, with a mean age of 58.5 ± 16.8 years, mean BMI of 25.07 ± 2.8 kg/m^2 and mean total severity score of 3.9 ± 1.0. There were no statistically significant differences in gender between the groups, while age ($p = 0.03$) and BMI ($p < 0.001$) were significantly higher in the severe/critical group. Compared to the ordinary group, patients in the severe/critical group had more chronic diseases such as diabetes mellitus (70% vs 23%; $p < 0.001$) and dyslipidemia (70% vs 30%; $p < 0.001$). On the contrary, the presence of hypertension was not significantly different between the two groups ($p = 0.30$). The severe/critical group had a higher prevalence of patients requiring admission to the ICU than the ordinary case group (73% vs 20%; $p < 0.001$).

Baseline clinical characteristics of patients are detailed on Table 1; categorical variables statistically associated with the two groups are listed in Table 2.

Epicardial adipose tissue volume

EAT volume was significantly higher in severe/critical group, compared with the ordinary group (151.4 ± 66.2 cm^3 vs 92.3 ± 44.4 cm^3, respectively; $p < 0.001$) (Fig. 2). Analysis of the ROC curve (Fig. 1) showed an area under the curve (AUC) of 0.781 ($p < 0.0001$; *CI* 95%: 0.662–0.900), which is an indication of good precision of the test. The cut-off value of 97 cm^3 obtained the highest Youden index, with 83.3% sensitivity and 70% specificity for predicting severe/critical manifestation CT of SARS-CoV-2 pneumonia (Fig. 3). Table 3 summarizes the sensitivity and specificity of different EAT volume values measured to predict severe/critical CT manifestation of SARS-CoV-2 pneumonia. Most patients in the severe/critical group (83.3%) have EAT volume ≥ 97 cm^3 and most patients in the ordinary group (7%) have EAT volume < 97 cm^3 (Fig. 4). The risk (odds ratio) of belonging to the severe/critical group in this population due to EAT ≥ 97 cm^3 is 11.667, with a 95% *CI* of 3.384–40.220 and a *p*-value < 0.001 (Table 4). Finally, Pearson's chi-square test showed a moderate association between EAT volume and ICU admission, with a Cramer's V value of 0.603 ($p < 0.001$). Percentage of ICU admission was higher in patients with EAT volume ≥ 97 cm^3 than in patients with EAT volume < 97 cm^3 (Fig. 5).

Table 2 Categorical variables

Categorial variable	*p*-value	Cramer's V	Association
Diabetes	< 0.001	0.468	Moderate
Dyslipidemia	0.002	0.400	Moderate
Consolidations	< 0.001	0.700	Strong
Crazy paving	< 0.001	0.778	Strong
Septal thickening	< 0.001	0.567	Moderate
ICU	< 0.001	0.439	Moderate
IMV	< 0.001	0.500	Moderate

Table 1 Characteristics of severe/critical group and ordinary group

Variable	Severe/critical group	Ordinary group	*p*-value
Age	66.83 ± 11.72	58.57 ± 16.86	0.031
Gender (M/F)	24 (80%)/6 (20%)	23 (77%)/7 (23%)	0.754
BMI	27.77 ± 2.11	25.07 ± 2.80	< 0.001
Diabetes (no/yes)	9 (30%)/21 (70%)	23 (77%)/7 (23%)	< 0.001
Hypertension (no/yes)	14 (47%)/16 (53%)	18 (60%)/ 12 (40%)	0.301
Dyslipidemia (no/yes)	9 (30%)/21 (70%)	21 (70%)/9 (30%)	0.002
ICU admission (no/yes)	11 (37%)/19 (73%)	24 (80%)/6 (20%)	0.001
Total severity score	15.00 ± 2.21	3.97 ±1.03	< 0.001
Consolidations (no/yes)	4 (13%)/26 (87%)	25 (83%)/25 (17%)	< 0.001
Crazy paving (no/yes)	6 (20%)/24 (80%)	29 (97%)/1 (3%)	< 0.001
Septal thickening (no/yes)	7 (3%)/23 (77%)	24 (80%)/6 (20%)	< 0.001
EAT volume	151.40 ± 66.22	92.35 ± 44.46	< 0.001

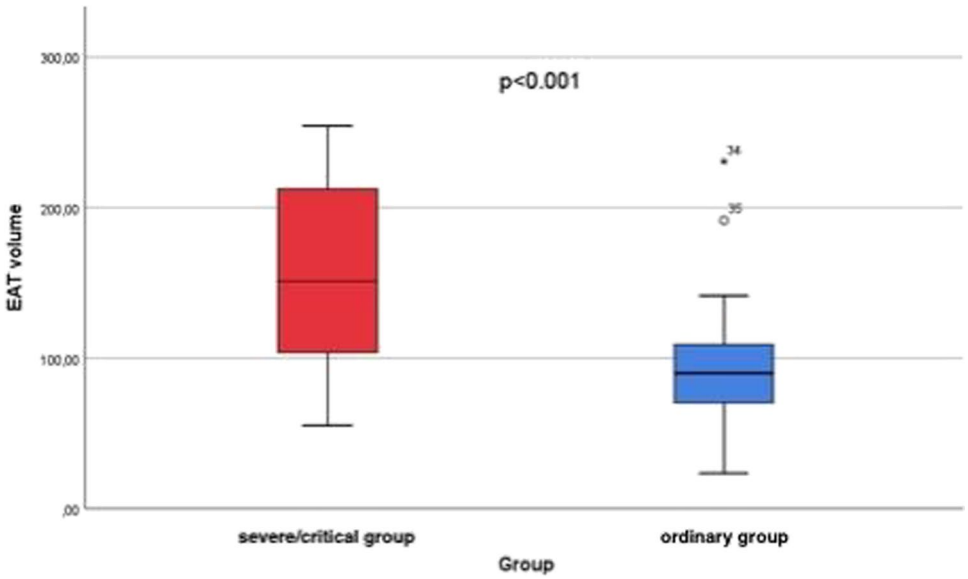


Fig. 2 Boxplot shows differences in EAT volume in severe/critical group and in ordinary group

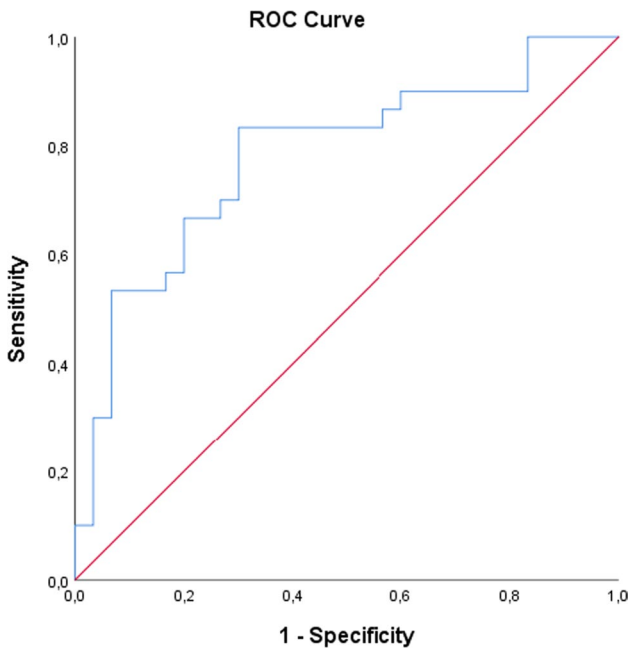


Fig. 3 Receiver-operating characteristic curve of EAT volume for predicting clinical severity of COVID-19 pneumonia. The overall accuracy of EAT volume for predicting a worse outcome was high with an area under the curve (AUC) of 0.781 ($p < 0.001$; *CI* 95%: 0.662–0.900). The cut-off value of 97 cm^3 had a sensitivity of 83.3% and a specificity of 70%

Table 3 Sensitivity and specificity of different values of EAT volume measured by CT for predicting worse manifestation of SARS-CoV-2 pneumonia based on analysis of the receiver operating curve

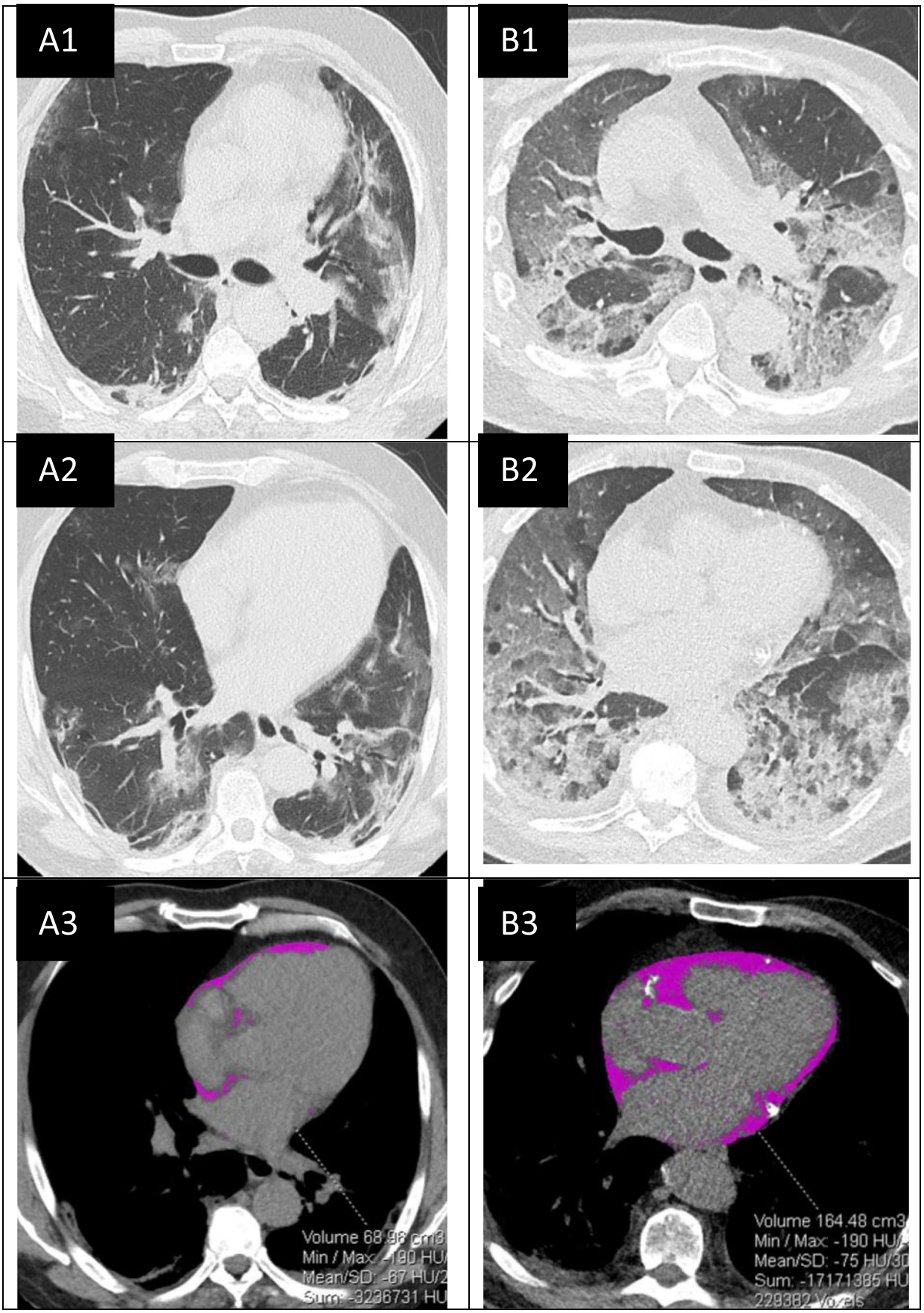
Positive if greater than or equal to[a]	Sensitivity	1 — specificity	Youden Index
90,0600	0.833	0.500	0.333
91,0350	0.833	0.433	0.400
92,9250	0.833	0.400	0.433
94,6150	0.833	0.367	0.467
95,2550	0.833	0.333	0.500
96,7950	0.833	0.300	0.533
98,6350	0.800	0.300	0.500
101,5350	0.767	0.300	0.467
104,7150	0.733	0.300	0.433
105,7450	0.700	0.300	0.400
106,1400	0.700	0.267	0.433

Discussion

In this study, the relationship between EAT volume quantified by chest CT scan and the extent of SARS-CoV-2 pneumonia was examined.

Previous studies have shown that EAT volume is greater in patients with obstructive pulmonary disease and that it is independently associated with important modifiable cardiovascular risk factors [11, 17]. Additionally, several studies have recently associated EAT measures with COVID-19 severity and adverse clinical outcomes [18–21]. In particular, the hypothesis has been advanced that EAT volume could help in the stratification of prognostic risk of patients with COVID-19 [22]. In particular, the integration of EAT volume into the clinical risk score for patients with COVID-19 can potentially improve the prediction of adverse outcomes.

In this study, our aim was to determine an EAT volume value that could predict increased pulmonary involvement in SARS-CoV-2 pneumonia. In particular, EAT volume ≥ 97 cm^3 has been shown to be associated with a


A1
B1
A2
B2
A3
B3
Volume 68.98 cm3
Min / Max: -190 HU
Mean/SD: -67 HU/2
Sum: -3236731 HU
Volume 164.48 cm3
Min / Max: -190 HU
Mean/SD: -75 HU/3
Sum: -17171385 HU
229382 Voxels

◂**Fig. 4** Chest CT images and EAT evaluation in patients with SARS-CoV-2 pneumonia. Case A, patient aged 60–70 years included in ordinary group (total severity score < 7): **A1** CT image of the thorax passing through a plane below the tracheal carina showing ground glass opacity with thickening of the interstitial septa especially in the left lung. **A2** Plane passing through the lung bases showing ground glass opacity with patchy consolidation. **A3** The volume of the EAT, highlighted as a pink area, was 68.96 cm3. Case B, patient aged 70–80 years included in the severe/critical group (total severity score > 7): **B1** CT image of the chest passing through a level below the carina showing ground glass opacities bilaterally extended to the pulmonary parenchyma with thickening of the inter- and intralobular septa. **B2** Plan passing through the pulmonary bases which also shows pulmonary consolidations associated with some aspects of crazy paving: typical imaging findings of extensive pulmonary involvement in COVID-19. **B3** The volume of epicardial adipose tissue, highlighted as a pink area, was 164.48 cm3, much larger than that shown in case A

risk of a greater extent of COVID-19 pneumonia and ICU admission.

Although, to the best of our knowledge, no meta-analysis has yet defined normal and pathological values for the volume of EAT quantified by CT, the results of our study are similar to those of previous studies [23, 24]. Currently, there is no general consensus regarding the identification of a normal range for EAT volume [25, 26]. In a recent study, it was observed that EAT volume was positively associated with metabolic syndrome in patients with EAT > 100 ml [27]. In a study by Milanese et al., it was observed that diabetic patients had EAT volume values above the 100 ml threshold, unlike non-diabetic patients who were mostly below that value [28]. Furthermore, a recent systematic review of the literature by Spearman et al. reported values of CT-assessed EAT above 125 ml to be indicators of cardiac pathology [29]. This could suggest that EAT represents a metabolically active tissue characterized by volumetric changes due to metabolic and infectious conditions [30]. The release of proinflammatory cytokines from EAT into the general bloodstream may contribute to systemic inflammatory state in COVID-19 patients [20, 31]. Systemic inflammation, in turn, promotes the accumulation of EAT [32]. This local inflammation may explain the association of the EAT increase with the quantitative burden of COVID-19 pneumonia in our study.

In our study, compared to the ordinary group, the severe/critical group had significantly higher BMI values. The association between obesity and predisposition to viral pathogen infections, including SARS-CoV-2, has already been

Table 4 Distribution of subjects in the two groups by EAT volume

	Severe/critical group	Ordinary group	Odds ratio: 11.667
EAT volume < 96.795	5 (16.7%)	21 (70.0%)	95% *CI*: 3.384–40.220
EAT volume ≥ 96.795	25 (83.3%)	9 (30.0%)	$p < 0.001$

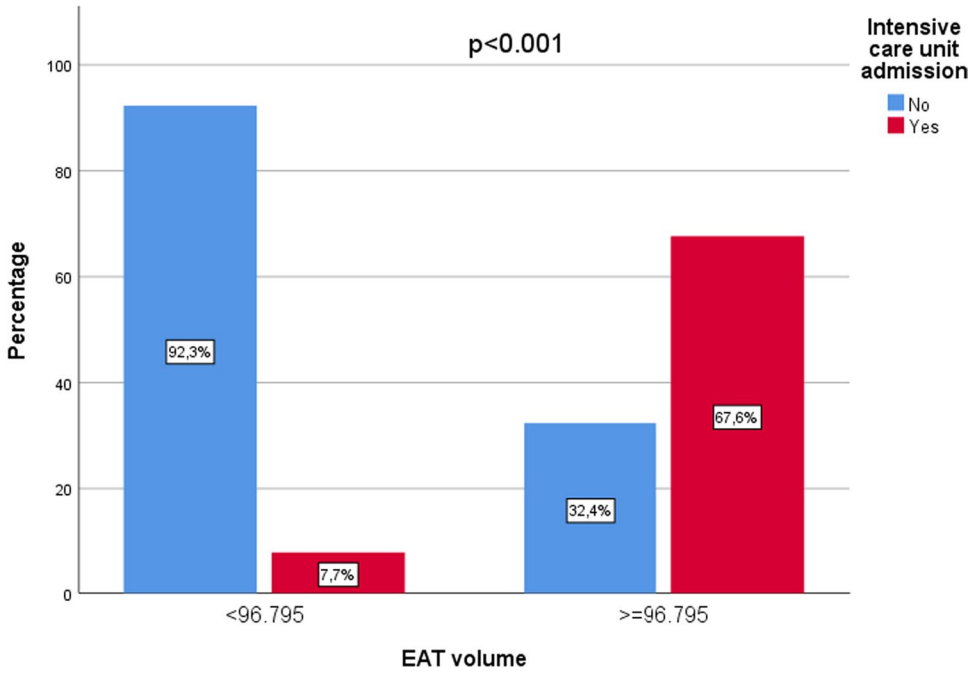


Fig. 5 The need for ICU admission was greater in patients with EAT volume ≥ 97 cm^3

documented in previous studies, identifying obesity as a risk factor for hospitalization and need for mechanical ventilation [7].

Our study has several limitations. First, complete clinical information could not be obtained for a minority of patients due to the nature of the retrospective study. Anamnestic and demographic information was retrieved from radiological reports and medical record review. Second, the interpretation of the patients' chest CT scans was performed by a single operator, however many previous studies have shown excellent interobserver agreement, suggesting the reliability and good reproducibility of the epicardial fat quantification procedure. Third, multivariate analysis for EAT volume and associated comorbidities was not performed; therefore, our results will need to be confirmed by further larger multicenter studies.

In conclusion, these findings suggest that epicardial adipose tissue volume may play an important role in the development of a worse burden of COVID-19 pneumonia. In this context, EAT may represent an important imaging biomarker that can predict a worse burden of SARS-CoV-2 pneumonia. Furthermore, EAT volume could also inspire future research on potential therapeutic implications. In particular, as previously suggested, EAT in addition to being a diagnostic parameter could also represent a clinically measurable and modifiable therapeutic target by drugs that modulate adipose tissue, such as ACE inhibitors, dipeptidyl peptidase 4 (DPP4) inhibitors, and statins, usually indicated in patients with diabetes and metabolic syndrome and recently shown to be involved in the pathogenesis of COVID-19 pneumonia [33–35].

The EAT parameter quantified by chest CT scan could provide an aid in the stratification of clinical risk in COVID-19 patients. However, further prospective multicenter studies are needed to determine whether EAT volume ≥ 97 cm^3 is applicable to different COVID-19 populations.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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